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CASE REPORT

Case Report: Treatment of systemic mastocytosis with sunitinib [version 1; peer review: 3 approved]

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Abstract

Mast cell activation disease typically presents as chronic multisystem polymorbidity of generally inflammatory ± allergic theme. Presently, treatment of the rare, cytoproliferative variant systemic mastocytosis employs empirically selected therapies to impede mast cell mediator production and action and, when necessary, inhibition of proliferation. Some tyrosine kinase inhibitors (TKIs) have been used successfully in uncommon cases of systemic mastocytosis not bearing that disease's usual imatinib-resistant KIT^{D816V} mutation. Recently, sunitinib, a multi-targeted TKI, had been successful in a case of systemic mast cell activation syndrome. In addition, mast allergy is principally a mast cell activation phenomenon, and sunitinib has been shown helpful in controlling a murine model of oral allergy syndrome. Here, we present the first use of sunitinib in systemic mastocytosis.

Keywords

mast cell, systemic mast cell activation disease, systemic mastocytosis, sunitinib, tyrosine kinase inhibitors

Open Peer Review

Approval Status

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2. **Leonard Weinstock**, Washington University School of Medicine, St. Louis, USA

3. **Vicki Ratner** , Interstitial Cystitis Association of America (ICA), McLean, USA

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Molderings GJ:** Conceptualization, Data Curation, Formal Analysis, Investigation, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Afrin LB:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Hertfelder HJ:** Conceptualization, Investigation, Writing – Review & Editing; **Brettner S:** Conceptualization, Data Curation, Investigation, Writing – Review & Editing

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Introduction

Systemic mastocytosis (SM) represents the rare variant (prevalence in Europeans ranges between 0.3 and 13:100,000)^{reviewed in 1} of systemic mast cell activation disease (MCAD; [Table S1](#)). MCAD comprises a heterogeneous group of multifactorial, polygenic disorders characterized by aberrant release of variable subsets of mast cell (MC) mediators together with accumulation of either morphologically altered and immunohistochemically identifiable mutated MCs due to MC proliferation (SM and mast cell leukemia) or morphologically ordinary MCs due to decreased apoptosis (well-differentiated SM and systemic mast cell activation syndrome)^{for details, see 2}.

Due to its genetic and epigenetic roots, MCAD generally is regarded as incurable. Recent mutational studies^{reviewed in 3} revealed an individual pattern of genetic and epigenetic alterations for each patient, which may affect the receptor expression, and their intracellular signal transduction pathways. Hence, mediator formation and release as well as inhibition of apoptosis, and/or increase in proliferation, are determined by individual genetic and epigenetic conditions requiring a highly personalized therapy for the disease. In formal studies in SM patients, although some tyrosine kinase inhibitors (TKIs) reduced MC burden, as reflected by histological normalization in bone marrow and improved laboratory surrogate markers (e.g., blood tryptase level), at best only partial improvement of mediator-related symptoms was achieved⁴⁻⁷. Distinction in pathways in the MC that promote MC proliferation vs. mediator production/release may explain why TKIs reduce MC burdens and MC-driven symptoms to different degrees⁴⁻⁷. However, in some case reports, TKIs have been significantly effective at relieving symptoms. Thus, in spite of a potential for serious adverse effects of these drugs, therapeutic trials may be justified in individual cases at various stages in their courses. Possibly due to the causative mutations in multiple genes leading to simultaneous activation of multiple intracellular pathways, multi-targeted TKIs such as imatinib and sunitinib may be more effective than drugs which selectively downregulate only one intracellular pathway. Sunitinib has been shown to be helpful in a murine model of oral allergy syndrome, a disease likely rooted in aberrant MC activation⁸.

Case presentation

A 58-year-old man presented to our *Interdisciplinary Multicenter Research Group for Systemic Mast Cell Diseases* for therapy of his progressive aggressive systemic mastocytosis (ASM, [Table S1](#) and [Table S2](#)), diagnosed according to the WHO criteria ([Table S3](#)), which remained significantly symptomatic despite the use of drugs administered to reduce MC activation^{reviewed in 9} (prednisone, rupatadine, ranitidine, ascorbic acid, ketotifen, montelukast, omalizumab) and drugs administered to reduce mediator-related symptoms (omeprazole, candesartan, risedronic acid, clonidine, cholestyramine, tranexamic acid, metamizole). A previous therapeutic trial with methotrexate was unhelpful. As typical in SM, his full history is complex, and symptoms reported, and key laboratory results found, are

summarized in [Table 1](#). The only minimal elevation in tryptase in this case of not just SM but in fact *aggressive* SM illustrates the heterogeneity of SM/ASM.

Since recently sunitinib had been used successfully in a case of systemic mast cell activation syndrome¹⁰ ([Table S1](#)), we decided for an off-label trial with sunitinib. Sunitinib is a multi-targeted TKI (up to 313 potential kinase targets)^{reviewed in 9} which, in addition to KIT, also binds to PDGFR- α , PDGFR- β , VEGFR1, VEGFR2, VEGFR3, FLT3, CSF-1R, and RET, some of which are also expressed in MCs. The patient gave written informed consent to participate in the off-label therapeutic trial with sunitinib, which is approved to treat imatinib-resistant, largely KIT-mutation-driven gastrointestinal stromal tumor and other applications, but not yet systemic mastocytosis^{reviewed in 11}. For such a therapeutic trial, ethical approval is not necessary in Germany^a. There was no contra-indication for use of sunitinib in the patient, in particular no sign of abdominal aortic aneurysm. We now report the first use of sunitinib in systemic mastocytosis.

In a first attempt, the patient took 12.5 mg sunitinib once daily for 24 days. After just three days, the abnormal bleeding (e.g. intense gum bleeding) he had due to increased fibrinolysis, which is a typical symptom in MCAD^{12,13}, ceased. The multiple subcutaneous fibrotic nodules that had developed all over his body during his many years of SM became tender and movable in the skin. Although no other symptoms were improved and sunitinib did not prevent flares of the disease, the patient felt better subjectively, in particular with less fatigue. However, in parallel the body hair became depigmented (white) and there was a decrease both in the number of thrombocytes and in the amount of total protein in blood, whereas uric acid in the blood increased inducing gout ([Table 1](#)). At that point treatment with sunitinib was discontinued.

When the altered blood parameters had returned to the normal ranges 33 days later, the patient asked for a second treatment try. During that time, the positive effects of the first period of sunitinib use had vanished. This second treatment, again with 12.5 mg sunitinib once daily, lasted only 8 days, during which the same positive and negative effects occurred as during the first intake, so the second therapeutic trial had to be terminated, too. It is possible that an even lower dose of the drug (e.g., 6.25 mg, which would pose some (surmountable) challenges, since the lowest capsule dose available is 12.5 mg), might have provided equal benefit with less toxicity, especially in view of the many

^a In Germany, individual therapeutic trials are not regulated by law. They are not notifiable, and there is no register for it. It is recognized that the freedom of medical treatment also includes the individual therapeutic attempt. The freedom of medical treatment has a legal basis in sub-constitutional laws and in regulations of the German medical association. In the end it is based on the freedom to pursue an occupation guaranteed by article 12 subparagraph 1 of the German constitution.

Table 1. Symptoms and Key Laboratory Results.

Symptoms	Key Laboratory Results (normal range)
<p>Fatigue; malaise; asthenia; feeling cold much of the time; headache; word finding difficulties; "brain fog"; attention deficit disorder; sleep disruptions; body shivering; restless-leg-like symptoms; short-term myoclonus; high startle response; central coordination disorder; constant bilateral tinnitus; irritated eyes; nasal irritation and copious coryza; wheezing; irritated throat during flares; dyspnea; dry cough; desire to clear one's throat; formation of a viscous mucus; chest discomfort/heaviness; palpitations; hot flash; arterial hypertension; intermittent tachycardic sinus arrhythmias; secondary Raynaud's syndrome; "easy" bruising/bleeding; nausea; diarrhea; marked abdominal bloating; recurrent splenomegaly; hypercholesterolemia; heartburn; diffuse edema with weight gain for several days; diffusely migratory paresthesias and pain; rheumatoid arthritis-like symptoms; flushes; itching without rashes; mouth ulcers; intolerance of a large number of foods, gluten, lactose, and chemical substances; gastritis; colitis; osteoporosis; waxing/waning bilateral sore throat; chronic kidney failure grade 1; dermatographism; longitudinal ridging in all nails; mood disturbances; recurrent impaired vision</p>	<p>Mast cell clusters (>15 MCs) in gastro-intestinal biopsies; 14% were stained CD25-positive; somatic KIT^{D816V} mutation and alterations in KIT outside codon 816; Serum tryptase: 15.8 µg/L (normal range <11.5 µg/L);</p> <p>Recurrent spontaneous fractures; Recurrent hepatic dysfunction;</p> <p>Plasma heparin level progressively increasing since the time of diagnosis; Clotting factor VIII increased; Trigger-induced increase of leukotrienes in blood; Severe IgA-deficiency in blood and saliva; Waxing/waning low-titer autoantibodies without corresponding symptoms in the respective organs;</p> <p>Decrease of thrombocytes from 197,000/µL to 114,000/µL (normal range 150,000 – 350,000/µL) and of the amount of total protein in blood to 5.5 g/dL (normal range 6.60 – 8.70 g/dL) Increase in uric acid from 5.6 to 7.2 mg/dL (normal 3.4 – 7.0 mg/dL)</p> <p>Mutation analysis of genomic DNA of leukocytes from peripheral blood by next generation sequencing: germline mutations in coding sequences: TET2^{T1762V} (heterozygously) IL13^{Q144R} (homozygously) TP53^{P72R} (homozygously) SETBP1^{A222T, T226Sfs*8} (heterozygously)</p>

case reports now of imatinib-responsive SM showing remarkable sensitivity to doses of that drug far below what seems necessary in most other oncologic applications of the drug. Cyclic rather than continuous dosing of sunitinib was shown to be the optimal approach in the approved indications for that drug. It may be the same, albeit using a cycling pattern different than for oncologic/anti-neoplastic applications, might prove true with use of sunitinib in SM.

Conclusions

In conclusion, this ASM partially responded to sunitinib. However, in this patient toxicities outweighed limited benefits. A similar benefit-risk assessment of sunitinib was observed in a second patient with ASM (unpublished case; GJM). However, our findings do not rule out that therapeutic trials with sunitinib may

be reasonable in other SM patients whose disease is refractory to other TKIs.

Consent

Written informed consent for publication of his clinical details was obtained from the patient.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Supplementary material

Table S1. Classification of mastocytosis.

[Click here to access the data.](#)

Table S2. C-Findings = Indication of impaired organ function due to MC infiltration defining a SM as an aggressive SM.

[Click here to access the data.](#)

Table S3. WHO criteria defining *Systemic Mastocytosis*.

[Click here to access the data.](#)

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Vicki Ratner

Founder and President Emeritus, Interstitial Cystitis Association of America (ICA), McLean, VA, USA

First, I would like to clarify that I am a clinician, and not a researcher. I have an expertise in mast cells, in particular, mast cells and interstitial cystitis.

I believe that it is very important to publish case reports, particularly on a disease that is relatively rare, and little is known about. I applaud the authors in their efforts. This case report focuses on a patient with aggressive systemic mastocytosis (ASM). The drug used for treatment was sunitinib, which has been approved by the FDA for the treatment of renal cell carcinoma and imitinib-resistant gastrointestinal stromal tumors.

Sunitinib, an oral medication, is a multitargeted receptor tyrosine kinase (RTK) inhibitor, as opposed to imitinib, which is also an RTK inhibitor, but can only target one type of receptor. 20% of patients do not respond to imitinib, and 50% become resistant to this drug over time.

The most common side-effects of sunitinib include HTN, fatigue, stomatitis, neutropenia and thrombocytopenia. Other adverse events include weakness, diarrhea, nausea, anorexia, erythrocytosis (an increase in the mass of the RBC's) and yellow discoloration of the skin. In addition, the patient may develop hand-foot disease, also called acral erythema, where the palms of the hands and the soles of the feet become red, swollen, numb and cause the skin to peel off. Side-effects in patients using sunitinib occurred in 10% or less of cases, with the exception of HTN, which occurred with much higher frequency.

There has been only one previous successful case report using sunitinib for aggressive systemic mastocytosis in the European literature. Molderings, et al., reported that the patient experienced less fatigue, which made daily ADL's (activities of daily living) easier for the patient to perform. In addition, after treatment, the subcutaneous fibrous nodules became movable (as opposed to firmly attached to the underlying tissue) and the smaller nodules disappeared completely. It is unclear why the remaining nodules, now movable, became tender.

In this second case report, where sunitinib was also used to treat progressive aggressive systemic

mastocytosis, there were some benefits. The authors pointed out that the patient had complete resolution of his intense bleeding gums within just 3 days of treatment, and also reported less fatigue. The subcutaneous nodules also became movable and tender. However, the patients' body hair became white, and there was a decrease in the number of thrombocytes and total protein in the blood. The uric acid level increased to the point of causing gout. At this point, the authors agreed that the side effects outweighed the benefits, and the medication was discontinued.

There is one case report published by L. Afrin in 2015 about the use of sunitinib in a patient with Mast Cell Activation Syndrome (MCAS) here in the U.S. The patients' symptoms have completely resolved as long as she remains on the drug, and thus far she has had no side effects. It has been over a year now.

The cost of sunitinib (Pfizer) is extremely high - almost \$150,000 per year. Often, in the U.S., insurance companies have refused to pay for all or part of the costs of this drug, so the cost to the patient can be a tremendous burden. Sunitinib most likely costs less if the dose is lowered and used cyclically. Cyclical use (for example 4 weeks on followed by 2 weeks off) may actually decrease the side effects more than a lower daily dose. However, though cyclical use may be sufficient to control malignancy, it is unlikely that cyclical use would be sufficient to control dysfunctional mast cells, as in MCAS, which might quickly revert to a more symptomatic baseline state of inappropriate activation as soon as the plasma concentration of the drug drops below a therapeutic threshold.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 10 May 2018

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Leonard Weinstock

Washington University School of Medicine, St. Louis, MO, USA

Is the background of the case's history and progression described in sufficient detail?

The background in the Introduction section nicely details the challenges treating systemic mastocytosis. This disease has considerable morbidity based on mediator secretion by malignant mast cells. The discussion clarifies why reduction of mast cell burden by other drugs do not necessarily bring about symptomatic relief.

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

The case report second along with the tables provided excellent details that enable the reader to understand the scope of systemic mastocytosis in this subject, the severity of symptoms, and the challenges in treatment. The patient failed standard therapy for this disease and yet had significant relief with a new medical approach. The problematic side effect of gout might have been prevented by use of allopurinol.

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes. Further studies are warranted.

Is the case presented with sufficient detail to be useful for other practitioners?

Yes. There is excellent detail to understand the management of systemic mastocytosis.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am actively diagnosing and treating patients with mast cell activation syndrome.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 08 January 2018

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Michael Huber

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Systemic mastocytosis as one form of systemic mast cell activation disease usually is an incurable disease, which due to patient-specific genetic and/or epigenetic alterations requires a highly personalized therapy to mitigate consequences of mast cell proliferation and/or inflammatory activation. This also implies that a few patients might profit from a therapy, which usually is referred to as noneffective for the majority of patients. Therefore, for the practitioner the publication of such rare cases is important to allow for a potentially effective, though unusual therapy option.

The present case report by Molderings *et al.* offers a detailed description of a patient with aggressive systemic mastocytosis treated with the tyrosine kinase inhibitor (TKI) sunitinib as well as an objective statement about pros and cons of the treatment. Moreover, this case report offers important background knowledge on the current classification of primary mastocytosis (Suppl. Table S1), a list of C-findings = indications of impaired organ function due to mast cell infiltration defining a systemic mastocytosis as an aggressive systemic mastocytosis (Suppl. Table S2), and the WHO 2008 diagnostic criteria for systemic mastocytosis (Suppl. Table S3). These enable the reader to access this information important for the comprehension of this case report without obtaining the original literature.

The reviewer suggests the following changes/additions:

- a) In the description of the TKI sunitinib, the publication by Todd *et al.* (Todd JR, Becker TM, Kefford RF, Rizos H. Secondary c-Kit mutations confer acquired resistance to RTK inhibitors in c-Kit mutant melanoma cells. *Pigment Cell Melanoma Res.* 2013; 26: 518-526) should be added. It describes a melanoma cell subline with an additional T670I mutation in c-Kit, which shows resistance to the TKIs imatinib, nilotinib, and dasatinib, but responds to sunitinib.
- b) In Suppl. Table S3 (minor Criteria), the sentence "3. Activating KIT mutation at codon 816 in in marrow, blood, or extracutaneous organ(s)" should be changed to "3. Activating KIT mutation at codon 816 in marrow, blood, or extracutaneous organ(s)"

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biochemistry and molecular immunology, mast cell biology, signal transduction

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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