CASE REPORT

Case Report: Treatment of systemic mastocytosis with sunitinib
[version 1; referees: 2 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 KITD816V mutation. Recently, sunitinib, a multi-targeted TKI, had been successful in a case of systemic mast cell activation syndrome. In addition, most 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

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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; Brettners S: Conceptualization, Data Curation, Investigation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Molderings GJ, Afrin LB, Hertfelder HJ and Brettners S. Case Report: Treatment of systemic mastocytosis with sunitinib [version 1; referees: 2 approved] F1000Research 2017, 6:2182 (doi: 10.12688/f1000research.13343.1)

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

First published: 28 Dec 2017, 6:2182 (doi: 10.12688/f1000research.13343.1)
Introduction
Systemic mastocytosis (SM) represents the rare variant (prevalence in Europeans ranges between 0.3 and 13:100,000)
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 studies2 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 achieved2-7. 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 degrees2-7. 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 midostaurin 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 activation6.

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 activation6 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 syndrome9 (Table S1), we decided for an off-label trial with sunitinib. Sunitinib is a multi-targeted TKI (up to 313 potential kinase targets)8 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 Germany4. 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 MCAD2-3, 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 different degrees of SM/ASM.

4 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)                                                                 |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Fatigue; malaise; asthenia; feeling cold much of the time; headache;     | Mast cell clusters (>15 MCs) in gastro-intestinal biopsies;                                          |
| word finding difficulties; “brain fog”; attention deficit disorder;      | 14% were stained CD25-positive;                                                                      |
| sleep disruptions; body shivering; restless-leg-like symptoms;           | somatic KIT<sup>D816V</sup> mutation and alterations in KIT outside codon 816;                      |
| short-term myoclonus; high startle response; central coordination disorder| Serum tryptase: 15.8 µg/L (normal range <11.5 µg/L);                                                 |
| constant bilateral tinnitus; nasal irritation and copious coryza;        | Recurrent spontaneous fractures;                                                                    |
| wheezing; irritated throat during flares; dyspnea; dry cough; desire     | Recurrent hepatic dysfunction;                                                                      |
| to clear one’s throat; formation of a viscous mucus; ched discomfort/heaviness; | Plasma heparin level progressively increasing since the time of diagnosis;                         |
| palpitations; hot flash; arterial hypertension; intermittent tachycardic | Clotting factor VIII increased;                                                                      |
| sinus arrhythmias; secondary Raynaud’s syndrome; “easy” bruising/bleeding;| Trigger-induced increase of leukotrienes in blood;                                                  |
| nausea; diarrhea; marked abdominal bloating; recurrent splenomegaly;     | Severe IgA-deficiency in blood and saliva;                                                          |
| hypercholesterolemia; heartburn; diffuse edema with weight gain for several days; | Waxing/waning low-titer autoantibodies without corresponding symptoms in the respective organs; |
| diffusely migratory paresthesias and pain; rheumatoid arthritis-like     | 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) |
| symptoms; flushes; itching without rashes; mouth ulcers; intolerance of  | Increase in uric acid from 5.6 to 7.2 mg/dL (normal 3.4 – 7.0 mg/dL)                               |
| a large number of foods, gluten, lactose, and chemical substances;       | Mutation analysis of genomic DNA of leukocytes from peripheral blood by next generation sequencing: |
| gastritis; colitis; osteoporosis; waxing/waning bilateral sore throat;    | germline mutations in coding sequences:                                                             |
| chronic kidney failure grade 1; dermatographism; longitudinal ridging in | TET2<sup>I1762V</sup> (heterozygously)                                                              |
| all nails; mood disturbances; recurrent impaired vision                  | IL13<sup>D144F</sup> (homozygously)                                                                  |
|                                                                          | TP53<sup>P72R</sup> (homozygously)                                                                    |
|                                                                          | SETBP1<sup>T228T</sup>, T228S<sup>*8</sup> (heterozygously)                                          |

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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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?
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 (Sull. 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)”
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.

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

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

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