Treatment of Mastocytosis

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Disclosures

• AB science Co Founder, Consultant, Stock Holder, Research grants

• Novartis Research grants

• Celgene research grants
Definitions and Classifications
**Mastocytosis**

**Definition**
- Mast cell accumulation in various organs (Skin, GI tract, Liver, Bone and Bone Marrow, etc)

- Myeloproliferative disorder; Aggressive vs indolent disease

- Association with hematological disorders

- Clinical heterogeneity (Infiltration vs Mediators release)

<table>
<thead>
<tr>
<th>Children</th>
<th>Adult Young vs Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>Adult age onset</td>
</tr>
<tr>
<td>Frequent regression</td>
<td>Chronic disease</td>
</tr>
<tr>
<td>Reactive disease ?</td>
<td>No regression</td>
</tr>
<tr>
<td></td>
<td>Clonal disease</td>
</tr>
</tbody>
</table>

**Mast cell Leukemia and Sarcoma:**
Rare, Rapid Fatal outcome
Mastocytosis: Spectrum of the disease

Organopathy prominent

- Pre-diagnostic SM
- Indolent SM
- Smoldering SM
- Aggressive SM / SM + associated hematological malignancy
- Mast cell leukemia

Disease aggressiveness

Systemic mastocytosis in adults: 2015 update on diagnosis, risk stratification, and management

Animesh Pardanani1,3*

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Mastocytosis: Spectrum of the disease

Systemic mastocytosis in adults: 2015 update on diagnosis, risk stratification, and management

Animesh Pardanani

MCAS

Mast cell mediator symptoms prominent

- Skin: pruritus, flushing, hives
  - Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramps, heartburn
  - Cardiovascular: syncope, dizziness, palpitations
  - Neurologic: memory/cognitive difficulties, depression, headache, sleep disturbance

Anaphylaxis: (hypotension >> angioedema)
- Hymenoptera stings, drugs, food
- Bone: osteopenia, osteoporosis, osteoporotic fractures?, back pain, bone pain

Constitutional:
- Generalized weakness, fatigue, arthralgias, myalgias, sweats, chills

Ensure that organopathy is due to mast cell infiltration:
- Osteolysis w/ pathologic fractures
- Lymphadenopathy
- Splenomegaly/hypersplenism
- Hepatomegaly/ascites
- Cytopenias
- Malabsorption or protein-losing enteropathy w/ weight loss

Organopathy prominent

- Pre-diagnostic SM
- Indolent SM
- Smoldering SM?
- Aggressive SM / SM + associated hematological malignancy
- Mast cell leukemia

Disease aggressiveness
Updated WHO Classification of Mastocytosis 2016

Cutaneous mastocytosis (CM)
   - Maculopapular CM (MPCM) = urticaria pigmentosa (UP)
   - Diffuse CM (DCM)
   - Mastocytoma of skin

Systemic mastocytosis (SM)
   - Indolent SM (ISM)
   - Smoldering SM (SSM)
   - SM with associated hematologic neoplasm (AHN)*
   - Aggressive SM (ASM)
   - Mast cell leukemia (MCL)

Mast cell sarcoma

*The previous term SM-AHNMD (SM with clonal hematologic non-mast cell-lineage disease) and the new term AHN can be used synonymously.
Prognosis

Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors

Ken-Hong Lim, Ayalew Tefferi, Terra L. Lasho, Christy Finke, Mrinal Patnaik, Joseph H. Butterfield, Rebecca F. McClure, Chin-Yang Li and Animesh Pardanani
Prognosis

Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors

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Indolent Mastocytosis >80%

Aggressive Mastocytosis <20%
Diagnosis
Mastocytosis Diagnosis

1. DARIER ’ S SIGN FOR CUTANEOUS MASTOCYTOSIS (Skin involvement is not required)

2. HISTOLOGY FOR CUTANEOUS AND/OR SYSTEMIC MASTOCYTOSIS (required)
   - TOLUIDINE BLUE
   - ANTI-TRYPTASE STAINING
   - CD117+, CD2+ and/or CD25+, CD15-

3. MAST CELL MEDIATORS
   - Total tryptase >20ng/ml
   - Soluble C-kit level
Clinical and Biological investigations

- **Symptoms**: handicap fonctionnel, asthenia, prurit, flush, depression, diarrhea, pollakiuria, vascular instabilities

- **Clinical**: Weight-nutrition, Skin, tumoral syndrome (Lymph nodes, splenomegaly, hepatomegaly)

- **Biology**: CBC, Liver Enzymes, Albumin, tryptase, IgE, Vitamin D.

- **Organ infiltration**: skin biopsy, bone marrow, others (digestive tract, liver…). Bone marrow aspiration, Mast cell phenotype

- **Screening of c-kit mutation** (Skin, infiltrated organ, peripheral blood ?)

- **Bone check up**: X Ray in case of symptoms, Bone density+++.

- **Associated Hematological Neoplasm**
# Diagnosis Criteria and Classification

A firm diagnosis of systemic mastocytosis is established when at least 1 major and 1 minor or at least 3 minor criteria are present.

<table>
<thead>
<tr>
<th>Major</th>
<th>Multifocal dense infiltrates of MCs in bone marrow sections or other extracutaneous organs (&gt;15 MCs in aggregate).</th>
</tr>
</thead>
</table>
| Minor | a. MCs in bone marrow or other extracutaneous organs show an abnormal (spindle-shaped) morphology (>25%).  
      b. Mutation at codon 816 of the *KIT* gene in extracutaneous organs. In most cases the mutation is D816V.  
      c. MCs in bone marrow express CD2 and/or CD25.  
      d. Serum tryptase >20 ng/mL (not in patients with AHNMD-type disease). |
| B findings | a. Bone marrow biopsy showing >30% infiltration by MCs (focal, dense aggregates) and/or serum tryptase level >200 ng/mL.  
              b. Signs of dysplasia or myeloproliferation in non-MC lineages, but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts.  
              c. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging. |
| C findings | a. Bone marrow dysfunction manifesting as cytopenia (ANC <1.0 x 10⁹/L, Hb <10 g/dL, or platelets <100 x 10⁹/L), but no obvious non-MC hematopoietic malignancy.  
              b. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension.  
              c. Skeletal involvement with large osteolytic lesions and/or pathological fractures.  
              d. Palpable splenomegaly with hypersplenism.  
              e. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates. |
Physiopathology
Simplified pathways of human MC differentiation

**Tissues**
- MC_C
- MC_TC
- MC_T

**Circulation**
- SCF
- IL-4
- IL-6
- IL-10
- CD43
- CD13
- c-kit high
- FcεRI neg
- CD13

**Bone Marrow**
- Stem Cell
- CD34+

**Survival**
- SCF
- NGF
- IL-4
- IFN-γ
- ……
Simplified pathways of human MC differentiation

Tissues

Circulation

Bone Marrow

Stem Cell

CD34+

CD13+

FcεRI neg

IL-4

IL-6

IL-10

SCF

IL-4

SCF

Survival:

SCF

NGF

IL-4

IFN-γ

......

CD34+
c-kit high
Oncogenic Mutations of c-kit in Mastocytosis

Pediatric Mutations 75%
Clonal disease +++
Regression

Adult Mutations 85%
Clonal disease +++
No regression
Oncogenic Mutations of c-kit in Mastocytosis

Pediatric Mutations 75%
Clonal disease +++
No regression

Adult Mutations 85%
Clonal disease +++
Regression

Sarcoma
Adult

Oncogenic Signal

1

2
Oncogenic Mutations of c-kit in Mastocytosis

Pediatric Mutations 75%
Clonal disease +++
Regression

Adult Mutations 85%
Clonal disease +++
No regression

1

Oncogenic Signal

2

Sarcoma
Adult

Indolent
Vs
Aggressive?
AHN
MCL

Exons 8 to 11
Exon 17

WT
P-Kit
SRSF2-P95 Hotspot Mutation is Highly Associated with Aggressive Forms of Mastocytosis and Mutations in Epigenetic Regulator Genes

Katia Hanssens, Fabienne Brenet, Julie Agopian, Sophie Georin-Lavialle, Gandhi Damaj, Laure Cabaret, Maria Olivia Chandesris, Paulo de Sepulveda, Olivier Hermine, Patrice Dubreuil § and Erinn Soucie* (Haematologica; in press)
Mutations Hierarchy in Mastocytosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>ASM-AHNMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F50</td>
<td>SRSF2^{p95L}, SRSF2^{p95H}</td>
</tr>
<tr>
<td></td>
<td>SRSF2^{WT}</td>
</tr>
<tr>
<td></td>
<td>KIT^{WT}</td>
</tr>
<tr>
<td></td>
<td>TET2^{WT}</td>
</tr>
<tr>
<td></td>
<td>KIT^{D816V}</td>
</tr>
<tr>
<td></td>
<td>TET2^{Q1389*}</td>
</tr>
<tr>
<td>V20</td>
<td>SRSF2^{p95H}</td>
</tr>
<tr>
<td></td>
<td>SRSF2^{WT}</td>
</tr>
<tr>
<td></td>
<td>KIT^{WT}</td>
</tr>
<tr>
<td></td>
<td>TET2^{Q734*}</td>
</tr>
<tr>
<td></td>
<td>KIT^{M1800D}</td>
</tr>
<tr>
<td></td>
<td>TET2^{Q734*}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Disease subtype</th>
<th>BM mast cells, %</th>
<th>Serum trypase, μg/L</th>
<th>Mutation load of KIT^{D816V}, PB</th>
<th>KIT^{D816V} Mast cells</th>
<th>CD15⁺</th>
<th>TET2 mutation Mast cells</th>
<th>CD15⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>ASM-CMML</td>
<td>75</td>
<td>385</td>
<td>5</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>ASM-CMML</td>
<td>70</td>
<td>350</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>ASM-MDS/MPNu</td>
<td>70</td>
<td>120</td>
<td>48</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>ASM-MDS/MPNu</td>
<td>40</td>
<td>88</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>37</td>
<td>SM-CMML</td>
<td>20</td>
<td>30</td>
<td>0.4</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
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</table>
### Associated Hematological Malignancies

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHNMD; n (%)</strong></td>
<td>20 (33)</td>
<td>22 (33)</td>
<td>48</td>
<td>134 (40%)</td>
<td>62</td>
</tr>
<tr>
<td><strong>Myeloid %</strong></td>
<td>82</td>
<td>90</td>
<td>83</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td><strong>MDS %</strong></td>
<td>32</td>
<td>9</td>
<td>8</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td><strong>CMML %</strong></td>
<td>39</td>
<td>27</td>
<td>23</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>MPN %</strong></td>
<td>9</td>
<td>21</td>
<td>45</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>AL %</strong></td>
<td>10</td>
<td>21</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphoid %</strong></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td><strong>Lymphoma %</strong></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>MM %</strong></td>
<td>N=2</td>
<td>10</td>
<td>4</td>
<td>5 (MGUS)</td>
<td></td>
</tr>
<tr>
<td><strong>CLL %</strong></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
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</tr>
</tbody>
</table>

*Damaj et al, CEREMAST, Unpublished data*
## Genes mutations in Associated Hematological Malignancies

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>48</td>
<td>20</td>
<td>134</td>
<td>23</td>
<td>8</td>
<td>62</td>
</tr>
<tr>
<td><strong>D816; n(%)</strong></td>
<td>45 (94)</td>
<td>16 (80)</td>
<td>50 (63)</td>
<td></td>
<td></td>
<td>44 (86)</td>
</tr>
<tr>
<td><strong>JAK-2; n(%)</strong></td>
<td>na</td>
<td>na</td>
<td>6 (8)</td>
<td></td>
<td></td>
<td>2 (7.5)</td>
</tr>
<tr>
<td><strong>TET-2; n(%)</strong></td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>8 (35)</td>
<td>5 (62)</td>
<td>12 (32)</td>
</tr>
<tr>
<td><strong>ASXL1; n (%)</strong></td>
<td>na</td>
<td>na</td>
<td>na</td>
<td></td>
<td>2(25)</td>
<td>6 (17)</td>
</tr>
<tr>
<td><strong>FGFR4; n(%)</strong></td>
<td>na</td>
<td>na</td>
<td>na</td>
<td></td>
<td></td>
<td>7 (18)</td>
</tr>
<tr>
<td><strong>CBL; n(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(12.5)</td>
</tr>
</tbody>
</table>

- TET2, ASXL1 are positive, only in the myeloid AHNMD

*Damaj et al, CEREMAST, Unpublished data*
Elderly patients

130 patients (80 Men 50 Women)
Age 75 years [70-90]
ASXL1 but not TET2 mutations adversely impact overall survival of patients suffering systemic mastocytosis with associated clonal hematologic non mast cell diseases

Gandhi Damaj¹,²,³, Magalie Joris¹, Olivia Chandesris²,⁴, Katia Hanssens⁵, Erinn Soucie⁵, Danielle Canioni⁶, Brigitte Kolb⁷, Isabelle Durieu⁸, Emanuel Gyan⁹, Cristina Livideanu¹⁰, Stephane Chèze¹¹, Momar Diouf¹², Reda Garidi¹³, Sophie Georgin-Lavialle¹⁴, Vahid Asnafi¹⁵, Ludovic Lhermitte¹⁵, Christian Lavigne¹⁶, David Launay¹⁷, Michel Arock¹⁸,¹⁹, Olivier Lortholary²⁰, Patrice Dubreuil⁵* and Olivier Hermine²,³,⁴*
Overall frequency and prognostic impact of mutated genes in 70 advanced \textit{KIT} D816V+ SM patients

60% of patients had $\geq$2 mutated genes in addition to \textit{KIT} D816V

Overall survival in advanced SM depending on mutations in the \textit{SRSF2/ASXL1/RUNX1} (S/A/R) panel

Clinical and Molecular Based Risk Score

Jawhar et al., Leukemia 2016; 29
Evidence for Cognitive Impairment in Mastocytosis: Prevalence, Features and Correlations to Depression

Daniela Silva Moura¹,²*, Serge Sultan⁷,⁸, Sophie Georgin-Lavialle¹,³,⁴, Stéphane Barete¹,³,⁵, Olivier Lortholary¹,⁶, Raphael Gaillard⁹,¹⁰, Olivier Hermine¹,³,¹¹,¹²*

Depression in Patients with Mastocytosis: Prevalence, Features and Effects of Masitinib Therapy

Daniela Silva Moura¹,², Serge Sultan²,³, Sophie Georgin-Lavialle¹,⁴, Nathalie Pillet³, François Montestruc⁵, Paul Gineste⁶, Stéphane Barete⁶, Gandhi Damaj⁷, Alain Moussy⁵,⁷, Olivier Lortholary⁹, Olivier Hermine¹,³,⁴,⁵,¹²*

Mastocytosis and psychological stress
Alexythymia ++++
Cognitive functions impairment
Depression
Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases

Lawrence B. Afrin, Dieter Pöhlnau, Martin Raithel, Britta Haenisch, Franz L. Dumoulin, Juergen Homann, Uwe M. Mauer, Sabrina Harzer, Gerhard J. Molderings
Hyperperfusion of central grey nuclei:
11 patients with cognitive impairment vs 33 controls
Corelation with cognitive dysfunctions
Hypoperfusion of the anterior Cingulum antérieur
10 patients with depression and mastocytosis Vs. 18 patients with Mastocytosis but not depressed
Tryptophan metabolism and Mastocytosis

Georgin Lavialle et al, Molecular Psychiatry, 2016

Tryptophan

Serotonin
(5-hydroxytryptamine)

Melatonin

Histamine
Others

Histamine abnormalities

Proteases

Neurotoxicity
Oxidative stress
Apoptosis

Depression ?

Cognition (?)
Treatment
Therapeutic Decision

- **Agressive disease**: Reduction of life expectancy and organ failure

- **Indolent disease**: No life expectancy reduction, no organ failure, Handicap associated with symptoms (patient vs physician)
Treatment of Indolent Diseases
Identification of all systemic manifestations in patients suffering from mastocytosis

- From 2004, 363 mastocytosis patients and 90 controls in France were asked to rate their overall disability (OPA score) and the severity of 38 individual symptoms.

- A specific questionnaire (AFIRMM V1), encompassing these 38 symptoms, has been created and validated.

*PloS ONE. 2008 May 28;3(5):e2266*
Identification of all systemic manifestations in patients suffering from mastocytosis

Table 3. Disability by symptom: patients vs. controls.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rank</th>
<th>Controls</th>
<th>n</th>
<th>Any disability</th>
<th>Severe or intolerable disability</th>
<th>Patients</th>
<th>n</th>
<th>Any disability</th>
<th>Severe or intolerable disability</th>
<th>P-value</th>
<th>Any disability</th>
<th>Severe or intolerable disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological impact</td>
<td>1</td>
<td>90</td>
<td>9</td>
<td>(10%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>261</td>
<td>(72%)</td>
<td>120 (33%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>2</td>
<td>90</td>
<td>34</td>
<td>(38%)</td>
<td>3 (3%)</td>
<td>362</td>
<td>296</td>
<td>(82%)</td>
<td>102 (28%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>90</td>
<td>25</td>
<td>(28%)</td>
<td>3 (3%)</td>
<td>363</td>
<td>299</td>
<td>(82%)</td>
<td>82 (23%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Food allergy/intolerance</td>
<td>4</td>
<td>90</td>
<td>9</td>
<td>(10%)</td>
<td>0 (0%)</td>
<td>363</td>
<td>222</td>
<td>(61%)</td>
<td>97 (27%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Erythematous crisis</td>
<td>5</td>
<td>90</td>
<td>17</td>
<td>(19%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>293</td>
<td>(81%)</td>
<td>69 (19%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Muscle and joint pain, cramps</td>
<td>6</td>
<td>90</td>
<td>36</td>
<td>(40%)</td>
<td>3 (3%)</td>
<td>363</td>
<td>276</td>
<td>(76%)</td>
<td>71 (20%)</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>7</td>
<td>90</td>
<td>58</td>
<td>(64%)</td>
<td>6 (7%)</td>
<td>362</td>
<td>263</td>
<td>(73%)</td>
<td>64 (18%)</td>
<td>0.12</td>
<td>0.0098</td>
<td></td>
</tr>
<tr>
<td>Drug allergy</td>
<td>8</td>
<td>90</td>
<td>16</td>
<td>(18%)</td>
<td>0 (0%)</td>
<td>363</td>
<td>205</td>
<td>(56%)</td>
<td>70 (19%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Aerophobia/eructation</td>
<td>9</td>
<td>90</td>
<td>43</td>
<td>(48%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>229</td>
<td>(63%)</td>
<td>62 (17%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Dyspnea/bronchoreactivity</td>
<td>10</td>
<td>90</td>
<td>15</td>
<td>(17%)</td>
<td>3 (3%)</td>
<td>362</td>
<td>154</td>
<td>(43%)</td>
<td>94 (26%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>90</td>
<td>34</td>
<td>(38%)</td>
<td>4 (4%)</td>
<td>362</td>
<td>250</td>
<td>(69%)</td>
<td>48 (13%)</td>
<td>&lt;0.0001</td>
<td>0.0190</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>12</td>
<td>90</td>
<td>16</td>
<td>(18%)</td>
<td>0 (0%)</td>
<td>363</td>
<td>196</td>
<td>(54%)</td>
<td>65 (18%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Reduced sexual relations</td>
<td>13</td>
<td>90</td>
<td>11</td>
<td>(12%)</td>
<td>4 (4%)</td>
<td>362</td>
<td>132</td>
<td>(36%)</td>
<td>65 (18%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0014</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>14</td>
<td>90</td>
<td>35</td>
<td>(39%)</td>
<td>2 (2%)</td>
<td>362</td>
<td>249</td>
<td>(69%)</td>
<td>40 (11%)</td>
<td>&lt;0.0001</td>
<td>0.0100</td>
<td></td>
</tr>
<tr>
<td>Ocular discomfort</td>
<td>15</td>
<td>90</td>
<td>43</td>
<td>(48%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>219</td>
<td>(60%)</td>
<td>55 (15%)</td>
<td>0.0309</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Memory loss</td>
<td>16</td>
<td>90</td>
<td>32</td>
<td>(35%)</td>
<td>0 (0%)</td>
<td>362</td>
<td>240</td>
<td>(66%)</td>
<td>34 (9%)</td>
<td>&lt;0.0001</td>
<td>0.0025</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>17</td>
<td>90</td>
<td>29</td>
<td>(32%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>166</td>
<td>(46%)</td>
<td>47 (13%)</td>
<td>0.0205</td>
<td>0.0011</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>17</td>
<td>90</td>
<td>29</td>
<td>(32%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>166</td>
<td>(46%)</td>
<td>47 (13%)</td>
<td>0.0205</td>
<td>0.0011</td>
<td></td>
</tr>
</tbody>
</table>
Symptomatic Therapies of Mastocytosis

Eviction of mast cells stimulants: depend on the patient history

Aim at inhibiting mediator release by mast cell or mediators effects.

- **Anti-H1**: pruritus, flush and sometimes GI pains.
- **Anti-H2**: essentially GI pains.
- **Aspirin**: for flushing, tachycardia, but may cause vascular collapse!!!
- **Corticoids**: for local treatment of cutaneous lesions, ascite, malabsorption, GI cramps (budesonide: corticoïde à délitément entéral)
- **Cromoglycate disodium**: non specific mediator release symptoms
- **Anti-leucotriènes** (montelukast-singulair): for respiratory manifestations
- **Epinephrin**: Hypotension
- **Biphosphonates**: bone pain and bone loss
ITK for indolent diseases

- New ITK
- Inhibiton of Mast cell activation (c-kit, Lyn, Fyn, etc)
- Cytoreductive on Mast cells (optional ++)
- Not cytoreductive on other cells
- Not toxic (short term and long term)
  - Genotoxic, carcinogenic
  - Cardiotoxic (Abl++, Src, VEGF, Herg channel, etc)
Masitinib (AB1010), a Potent and Selective Tyrosine Kinase Inhibitor Targeting KIT

Patrice Dubreuil¹,²,³,⁴*, Sébastien Letard¹,²,³,⁴, Marco Ciufolini⁴,⁵, Laurent Gros⁴, Martine Humbert⁴, Nathalie Castéran⁴, Laurence Borge¹,²,³, Bérengère Hajem⁴, Anne Lermet⁴, Wolfgang Sippl⁶, Edwige Voisset¹,²,³, Michel Arock⁷, Christian Auclair⁴,⁷, Phillip S. Leventhal⁴, Colin D. Mansfield⁴, Alain Moussy⁴, Olivier Hermine⁴,⁸*
Masitinib – Kinase inhibitory activity profile

Masitinib is a tyrosine kinase inhibitor that target mast cells and macrophages.

Kinase Inhibition Profile of Masitinib

<table>
<thead>
<tr>
<th>Target</th>
<th>IC₅₀ [nM]</th>
<th>Kd [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT wild-type (WT)</td>
<td>200</td>
<td>0.008</td>
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<tr>
<td>FYN</td>
<td>240</td>
<td>0.14</td>
</tr>
<tr>
<td>LYN</td>
<td>225</td>
<td>0.061</td>
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<tr>
<td>D816V KIT (exon 11)</td>
<td>5,000</td>
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<tr>
<td>KIT mutation (exon 17)</td>
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<tr>
<td>MCSFR-1</td>
<td>90</td>
<td>0.0076</td>
</tr>
<tr>
<td>PDGFRb</td>
<td>300</td>
<td>0.0084</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>50</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

Case Report in Dog Mast Cell Tumor

DAY 0

DAY 3

DAY 18