Diagnosis and Management of Patients with Mastocytosis

Peter Valent

ECNM Homepage Update 2013

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www.ecnm.net
PAUL EHRLICH (1854-1915)

- dye stains
- mast cells
- side chain theory
- magic bullets

modern hematology & immunostaining
mast cell & mastocytosis research
cell surface receptors
targeted drugs

2013
2015

1869 - Nettelship Rare Form of Urticaria
1878 - Sangster Urticaria Pigmentosa UP
1879 - Ehrlich Mast Cells (Mastzellen)
1887 - Unna Mast Cells in UP
1949 - Ellis Systemic Mastocytosis
1966 Ishizakas Detection of IgE etc
1979 - Lennert Kiel Classification
1991 - Metcalfe Consensus Classification
1995 - Nagata KIT D816V in SM
1998 - Escribano CD2/CD25 on MC in SM
1990-2000 Criteria Established
2000 Working Conference
2001 WHO Classification
2002 ECNM

HISTORY: MAST CELLS and MASTERS
History 1990 - 2000 - 2002 - 2011

WHO Classification of Tumors; IARC Press Lyon 2001

Multicenter Trials to determine disease related markers and criteria 1995-2000

WHO - Year 2000 Working Conference on Mastocytosis – Vienna

WHO Consensus Classification

WHO Classification of Tumors; IARCPress Lyon 2001

ECNM – European Competence Network on Mastocytosis 2002


Activities in the ECNM:
- Annual Meetings (9)
- Centers (25)
- Publications (20)
- Homepage

www.ecnm.net
ECNM – THE EUROPEAN COMPETENCE NETWORK ON MASTOCYTOSIS

Multi-Center European Initiative to
- Improve Recognition, Diagnosis & Therapy in Mastocytosis
- Provide all available Information to Patients and Doctors
- Study the Incidence and Epidemiology of Mastocytosis
- Start Cooperative Research-Projects on Mastocytosis in Europe
- Prepare and Conduct Clinical Trials
- ECNM Registry

www.ecnm.net
ECNM – Structure and Centers

Annual ECNM Meeting 2013: London (Sep 19-21)

Structure of the ECNM: Center Types

1) Center of Excellence
- Referal Center for all Patients
- All Major Diagnostics available
- All types of Therapy offered
- At least one COE per country = Aim
- Typical 3-4 Departments cooperate

2) Reference Center
- Focus on one major aspect
- Referal Center for Material etc
- Assists in developing Standards
- Usually Major Research Center
MAST CELLS FORM A UNIQUE LINEAGE WITHIN THE HEMATOPOIETIC SYSTEM

**PAUL EHRLICH (1854-1915)**

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- magic bullets

**Mast Cells**
- KIT+
  - IL-3R-
  - IL-4R+
- IgER+
- Histamine+
- Tryptase+
- Chymase+/-
- Heparin+
- Basogranulin-
- CD63+
- CD203c+/-

**Basophils**
- KIT-
  - IL-3R+
  - IL-4R+
- IgER+
- Histamine+
- Tryptase+/-
- Chymase+/-
- Heparin-
- Basogranulin+
- CD63+
- CD203c+

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2013
DIFFERENTIATION OF MAST CELLS

bone marrow endothelium vessel endothelium tissue

CD34+ progenitor

KIT
ILs, CSFs
SCF IL-6
bone marrow mast cell

circulating CD34+, KIT+ progenitor cell

SCF

mature tissue mast cells

IL-4

SCF

IL-6
Cutaneous Mastocytosis (CM) vs Systemic Mastocytosis (SM)!

Mostly Children ($KIT$mut $\approx 40\%$)

- Diagnosis: Skin only
- Biopsy of Skin
- Serum Tryptase
- Usually no BM Biopsy

Cutaneous Mastocytosis

Mostly Adults ($KIT$ D816V)

- Diagnosis: $>80\%$!
- Biopsy of BM (and Skin)
- Apply SM Criteria
- Define SM Variant

Systemic Mastocytosis

Hartmann. & Henz, Br J Derm 2001;144:682
Wolff et al, Leuk Res 2001;25:519
WHO CLASSIFICATION

- Cutaneous Mastocytosis (CM)
- Indolent Systemic Mastocytosis (ISM)
- SM with an Associated Hematologic non Mast Cell Lineage Disease (SM-AHNMD)
- Aggressive Systemic Mastocytosis (ASM)
- Mast Cell Leukemia (MCL)
- Mast Cell Sarcoma (MCS)
- Extracutaneous Mastocytoma
WHO Classification: Criteria for Systemic Mastocytosis (SM-Criteria)

Major Criteria
- Multifocal dense mast cell (MC) infiltrates (≥15 MC/infiltrate) in the bone marrow or in another extracutaneous organ

Minor Criteria
- >25% spindle-shaped cells in MC-infiltrates; or >25% of all MC are atypical MC (type I and/or type II) in bone marrow smears
- Expression of CD2 and/or CD25 in bone marrow MC
- Serum tryptase level >20 ng/ml (does not count in cases with an AHNMD)
- KIT point mutation at codon 816 (mostly D816V) in bone marrow or in another extracutaneous organ

The diagnosis Systemic Mastocytosis is established if at least 1 major and 1 minor or 3 minor criteria are fulfilled
Analysis of Bone Marrow Sections: Tryptase-Immunohistochemistry

Systemic Mastocytosis

SM-AHNMD ? Myelomastocytic ?
Bone Marrow Smear: Atypical Mast Cells in Systemic Mastocytosis

Criteria for Atypical Mast Cells Type I in Bone Marrow Smears:
A: Oval Nucleus, B: Cytoplasmic Extensions, C: Hypogranulated (2/3)

Sperr et al, Leuk Res 2001;25:529
Bone Marrow Smear: Atypical Mast Cells Type II and Metachromatic Blasts

Atypical Mast Cells Type II = Promastocytes in Bone Marrow Smears

Sperr et al, Leuk Res 2001;25:529

Metachromatic Blasts in Bone Marrow Smears
Mast Cell Numbers in Bone Marrow Smears in Patients with SM: Clinical Significance

Survival of patients with varying percentages of mast cells (of all nucleated cells) in bone marrow smears:

- ≥10%
- <10%

Survival of patients with varying percentages of pro-mastocytes (of all mast cells) in bone marrow smears:

- ≥10%
- <10%
Impact of the Mast Cell Count in the BM Smear in SM

BM Section IHC (tryptase)

80% survival: >20 years, alive

1% survival: <1 year (MCL)

BM smear

65%

35%
Impact of Mast Cell Morphology in Patients with MCL (>20% MC in BM Smears)

**Acute MCL:**
>20% MC in BM Smears
C-Findings

- Survival: <1 year

**Chronic MCL:**
>20% MC in BM Smears
No C-Findings

- Survival: >1 year

Hyperacute MCL
KIT D816H+
WHO Classification: Criteria for Systemic Mastocytosis (SM-Criteria)

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Minor Criteria

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The diagnosis Systemic Mastocytosis is established if at least 1 major and 1 minor or 3 minor criteria are fulfilled
Expression of CD2 and CD25 on Bone Marrow Mast Cells in a Patient with SM - Flow Cytometry

CD2 - FITC

CD117 - PE

CD25 - FITC

ISM
Detection of CD25 in Neoplastic Bone Marrow Mast Cells by Immunohistochemistry (IHC)

CD25-IHC:
- Simple Test
- Highly Specific (>95%) for neoplastic MC in SM
- MC in Myelomastocytic Leukemia & reactive MC Hyperplasia are CD25
- Highly Sensitive and superior to CD2
- IHC regarded equally diagnostic compared to flow-cytometry
WHO Classification: Criteria for Systemic Mastocytosis (SM-Criteria)

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The diagnosis Systemic Mastocytosis is established if at least 1 major and 1 minor or 3 minor criteria are fulfilled
Serum Tryptase Levels in Controls

Healthy controls:
Age: range 5-83 yrs

Serum tryptase levels:
Mean±S.D.: 5.7±2.7 ng/ml
Median: 5.2 ng/ml
Maximum: 18.2 ng/ml
Serum Tryptase Levels in various Groups of Patients with SM
Correlation Between Tryptase and Infiltration (grade) of the Bone Marrow by Neoplastic Mast Cells (Dense Tryptase+ Infiltrates)

$r=0.7$
Serum Tryptase Levels in Hematologic Disorders

1) Minor SM Criterion only
2) Does not Count as a Minor SM Criterion in Patients with AHNMD
WHO Classification: Criteria for Systemic Mastocytosis (SM-Criteria)

Major Criteria

- Multifocal dense mast cell (MC) infiltrates ($\geq 15$ MC/infiltrate) in the bone marrow or in an other extracutaneous organ

Minor Criteria

- $>25\%$ spindle-shaped cells in MC-infiltrates; or $>25\%$ of all MC are atypical MC (type I and/or type II) in bone marrow smears
- Expression of CD2 and/or CD25 in bone marrow MC
- Serum tryptase level $>20$ ng/ml (does not count in cases with an AHNMD)
- $KIT$ point mutation at codon 816 (mostly D816V) in bone marrow or in another extracutaneous organ

The diagnosis Systemic Mastocytosis is established if at least 1 major and 1 minor or 3 minor criteria are fulfilled
**KIT Point Mutations in Mastocytosis**

- **Proposed Standards (D816V)**
  - Bone marrow (bm) cells
  - MNC or unfractionated bm cells analyzed
  - Peripheral blood (MNC) should be analyzed in early screening (e.g. in pts with elevated tryptase only)
  - RT-PCR & RFLP or others (in D816V-negative patients → sequencing of KIT ?)

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**Diagram:**
- Exon 2
- Exon 8
- Exon 11
- Exon 17, 18
- Tyrosine kinase domain
- extracellular domains
- juxta-membrane helix regulatory point mutation (V560G, others)
- enzymatic pocket/activation loop activating point mutations (D816V, others)
- inactivating point mutation E839K
- COOH
<table>
<thead>
<tr>
<th>Mutation</th>
<th>Reported in</th>
<th>Frequency in SM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIT D816V</strong></td>
<td>all variants of SM also in cases of CM</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>KIT D816Y</td>
<td>ISM, SM-AHNMD, CM ?</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>KIT D816F</td>
<td>ISM, CM ?</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>KIT D816H</td>
<td>SM-AHNMD</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>KIT D812G</td>
<td>SM/ASM</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>KIT D560G</td>
<td>SM/ISM</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>KIT F522C</td>
<td>SM/ISM</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>KIT E839K</td>
<td>CM</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>KIT V531I</td>
<td>SM-AHNMD</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>KIT K509I</td>
<td>ISM/ASM</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
Stepwise Approach in Defining Subvariants of SM: Proposed Algorithm using WHO - Criteria

1 Major + 1 Minor or
3 Minor SM-Criteria

BM-Smear < 20% MC

FAB/WHO: No AHNMD

B-Findings

C-Findings

≥ 1 C

Myeloid Neoplasm

No B
No C

2/3 B but
No C

ISM

SSM

ASM

Eo↑ +

PDGFR-

B-Findings

C-Findings

≥ 1 C

Myeloid Neoplasm

No B
No C

2/3 B but
No C

ISM

SSM

ASM

Eo↑ +

PDGFR-

BM-Smear ≥ 20% MC

FAB/WHO: AHNMD

SM-AHNMD

FAB/WHO

FAB/WHO: AHNMD

PB-Smear <10% MC

PB-Smear ≥ 10% MC

Aleukemic MCL

MCL

Lymphoid Neoplasm

Myeloid Neoplasm

Others

SM-HES/CEL

SM-AML

SM-CMML

SM-MDS

Others

Eo↑ +

PDGFR-

Blasts ≥ 20%

Mono >1000 + Dysplasia

Dysplasia

Others
B-Findings (Borderline-Benign) and C-Findings (Consider Cytoreduction)

**B-Findings:**
- Infiltration grade (MC) in BM>30% and serum tryptase >200 (!) ng/ml
- Dysmyelopoiesis: Hypercellular marrow with signs of myelodysplasia or myelo-proliferation, but no criteria for MDS or MPN. Blood picture normal or slightly abnormal
- Organomegaly (without impairment of organ function): Hepatomegaly (without ascites), splenomegaly (palpable), lymphadenopathy (>2 cm in CT or US)

When 2 or 3 B-Findings but no C-Findings are recorded, the final diagnosis is Smouldering SM

**C-Findings:**
- One or more Cytopenias: ANC<1000/µl; Hb<10 g/dl; Plt<100000/µl
- Hepatopathy: Enlarged liver with ascites, elevated liver enzymes +/- portal hypertension
- Organopathy of Spleen: Splenomegaly with hypersplenism
- Malabsorption with hypalbuminemia and weight loss
- Large Osteolysis and/or severe Osteoporosis & pathologic fractures
What is a C-Finding: Guide for Daily Practice

**Typical Organopathy**

- Confirm Devastating Mast Cell Infiltration by Biopsy and Histology
- Exclude other Causes of Organopathy

And:

- rapid increase in serum tryptase?
- strong cytoplasmic expression of CD30?

Yes

C-Finding:

**C = Consider Cytoreduction**

Valent et al., Blood 2010;116:5812-7
Survival of Systemic Mastocytosis Patients – Mayo Experience

Summary

1) Patients with Indolent SM (ISM) have a normal life expectancy

2) Patients with ASM and SM-AHNMD have a poor survival

3) In patients with Mast Cell Leukemia (MCL) survival is usually < 1 year

4) The WHO Classification can safely discriminate between low risk and high risk mastocytosis patients

5) Treatment should therefore be adjusted to the WHO variant

Lim K et al. Blood 2009;113:5727-5736
PATHOGENETIC CONCEPT: ROLE OF OTHER DEFECTS

What factors and defects are responsible for SM and for the development of a high grade (mast cell-) disease in patients with *KIT D816V*+ SM?

? a) Cytokine Gene Polymorphisms b) KIT-independent signaling-pathways and molecules
What factors and defects are responsible for SM and for the development of a high grade (mast cell-) disease in patients with KIT D816V+ SM?

KIT-independent signaling molecules:
- Btk ? Lyn ?
- mutated RAS ?
- mutated TET2 ?
- mutated IgERβ ?

PATHOGENETIC CONCEPT: ROLE OF OTHER DEFECTS
Dasatinib counteracts phosphorylation of Btk in neoplastic mast cells

HMC-1.2

Mast cell leukemia (BM: 75% neoplastic MC)

Gleixner et al., Blood 2011;118;1885-1898
siRNA against Btk synergizes with midostaurin in counteracting the proliferation of HMC-1 cells

Dasatinib + PKC412
An Effective TKI Combination in KIT D816V+ Mast Cells

Gleixner et al., Haematologica 2007;92:1451

Gleixner et al., Blood 2011;118;1885-1898
Synergistic effects of TK inhibitors on growth of neoplastic mast cells

KIT G560V

KIT D816V

Combination Index values determined by calcusyn software

Gleixner et al, Blood 2006;107:752-759; Gleixner et al., Haematologica 2007;92:1451-1459
Effects of KIT TK inhibitors on growth of neoplastic mast cells (cell lines)

KIT D816V introduces resistance against imatinib

The Magic Bullets and Limitations

Gleixner et al, Blood 2006
Effects of KIT TK inhibitors on mediator release in human mast cells and basophils

The Magic Bullets and Limitations

![Graphs showing % histamine release vs anti-IgE concentration for mast cells and basophils, with different KIT TK inhibitors at various concentrations.](image-url)
Summary: TKI Effects on Mast Cells and Basophils relevant to Mastocytosis

1. **Imatinib** and most other TKI: show no relevant (beneficial) effects on KIT D816V+ Mast Cells

2. **Dasatinib**:
   a) Half Life too short to inhibit growth of MC
   b) Very low concentrations even promote IgE-dependent histamine release (clinically relevant?)

3. **Midostaurin (PKC412)**:
   a) Inhibits the growth of KIT D816V+ Mast Cells
   b) Inhibits IgE-dependent histamine release!
   c) Currently tested in clinical trials
   d) Will hopefully be approved for use in mast cell disorders in the future
Interim Analysis of the Global CPKC412D2201 Phase II Trial (Gotlib et al) – ASH 2012

- Midostaurin (2x100 mg per day orally) demonstrates a high rate of durable responses in advanced SM (single-arm Phase II Trial)
  - ORR 60% (> 50% of patients reached a major response)
  - ORR similar regardless of KIT D816V mutation status and # of prior therapies (IFN, 2CdA, imatinib, dasatinib, HU, ARA-C, others)
  - Reduction of serum tryptase levels and/or BM mast cell burden in ≈40% of patients indicates a potential for disease modification
  - > 50% response rate in MCL (historically has a dire prognosis)

- Median duration of response and median overall survival have not been reached with a median follow-up of 27 months
- Good tolerability with a safety profile consistent with prior studies
- The high response rate in Stage 1 permitted enrollment in the extension phase. Full accrual of 116 patients is now completed
Overall Survival in ASM/MCL

Survival (%)

All patients (n = 40)
ASM (n = 33)
MCL (n = 7)

Median duration of follow-up\(^a\): 27 months (range: 11-38)
\(^a\) Time from treatment start to data cut-off.

Deaths, n

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>ASM</td>
<td>12</td>
</tr>
<tr>
<td>MCL</td>
<td>3</td>
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</tbody>
</table>

Kaplan-Meier Estimate for Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
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<tbody>
<tr>
<td>ASM</td>
<td>Not reached</td>
</tr>
<tr>
<td>MCL</td>
<td>22.6 months</td>
</tr>
</tbody>
</table>

Gotlib et al, ASH 2012
# Treatment of Mastocytosis: Cytoreductive Drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISM (&gt;80%)</td>
<td><strong>NO cytoreductive treatment</strong> (exception: severe osteopenia with risk of pathologic fracture, life threatening recurrent shock?)</td>
</tr>
<tr>
<td>SSM</td>
<td><strong>Wait and watch</strong> in most cases. In select cases (with progression) consider IFNα, 2CdA, or targeted drugs</td>
</tr>
<tr>
<td>SM-AHNMD</td>
<td>Treat AHNMD as if no SM is present, and SM as if no AHNMD had been diagnosed (e.g. ASM-AHNMD !)</td>
</tr>
<tr>
<td>ASM with slow progression</td>
<td><strong>IFNα</strong> + glucocorticoids, 2CdA, in case of hypersplenism due to splenomegaly + MC infiltrates consider splenectomy (TKI in clinical trials, Imatinib only for rare KIT mutants)</td>
</tr>
<tr>
<td>ASM with rapid progression</td>
<td>Polychemotherapy with Fludarabine or 2CdA - in responding patients: consider stem cell transplantation</td>
</tr>
<tr>
<td>MCL</td>
<td>Polychemotherapy or 2CdA (IFNα or corticoids) - in responding patients: consider stem cell transplantation</td>
</tr>
</tbody>
</table>

In all categories, mediator-targeting drugs are given as adjunct to cytoreductive therapy.
Follow up in a Patient with Acute MCL

- WBC, G/L
- Tryptase, ng/ml

Day after start of induction therapy

Relapse

KIT

Diagnosis

Remission

Relapse
Cytoreductive and Anti-Mediator-Type Drugs

A: Cytoreductive Agents / Targeted Drugs

- Interferon alpha
- Glucocorticosteroids
- 2CdA
- TKI: PKC412, Dasatinib, Nilotinib

B: Anti-Mediator-Type Drugs

- Histamine Receptor Blockers
- Glucocorticosteroids
- Immunotherapy, anti-IgE, anti-IgER
- Bisphosphonates
- PKC412 (Dasatinib)
Thank you for your Attention

Peter Valent and Team

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Treatment of Patients with Mastocytosis

A: Treatment of Mediator-Related Symptoms:
   Drugs Targeting – Mediator Production
   – Mediator Release
   – Mediator Effects

B: Cytoreductive Therapy (SM+C-Finding/s)
   Drugs Targeting – Neoplastic Stem Cells
   – Progenitor Cells (IFNα)
   – Mast Cells
   – Specific Molecular Targets
Expression of CD52 on Neoplastic Mast Cells in Aggressive SM (ASM)
Established and Novel Diagnostic and Prognostic Markers in SM

Diagnostic Markers
- Tryptase
- KIT
- Chymase
- CD2
- CD25
- CD68R
- HDC
- CD30?

Prognostic Markers
- CD30?
- Btk?
- Lyn?
- CD2? (low levels in MCL)
- CD52? and CD123?
- IL-13 SNP?
- IL-4R SNP?
Expression of CD30 in MC in different SM variants: A new grading marker in SM?

ISM (CD30)  
![Image of ISM (CD30)]

SSM (CD30)  
![Image of SSM (CD30)]

MCL (CD30)  
![Image of MCL (CD30)]

IHC

SM, Systemic Mastocytosis  
ISM, Indolent SM  
SSM, Smouldering SM  
ASM, Aggressive SM  
MCL, Mast Cell Leukemia  
IHC, Immunohistochemistry  
BM, Bone Marrow  
MC, Mast Cells

classification of mast cell disease

- Normal BM MC
- Patient with ASM
Follow up in a Patient with ASM

- Prednisone
- Interferon-α
- 2CdA
- DAV
- Imatinib
- MCL
Follow up in Patients with ISM or SSM

Tryptase is the recommended Serum Marker in the Follow-Up of Patients With SM
Follow Up in Patients with ASM/SSM

a. ASM-CMML treated with IFNα-2b; b. SSM treated with Cladribine

**Graph a:**
- IFNα-2b, 3x10⁶U 3x/w + Apremisolon 25 mg
- Tryptase, ng/ml vs. Months

**Graph b:**
- 2CdA
- Anaphylactoid Shock
- Tryptase, ng/ml vs. Months
Phase II Trial ASM/MCL - Stanford Group
Jason Gotlib and Colleagues

- Midostaurin 100 mg po bid on 28-day continuous cycles for up to 12 cycles
- Formal response evaluated after 2 cycles; partial or major response per consensus criteria permit ongoing treatment
- Extension treatment beyond 12 cycles for patients with response and no > grade 3 toxicity related to midostaurin
- Dose reduction to 50 mg bid for > grade 3 hematologic or non-hematologic toxicity

Gotlib et al, ASH 2010
Histopathological Assessment

>50% Reduction in Marrow MC Burden by IHC (n=10)

IHC = MC tryptase - Immunohistochemistry
### Efficacy (Best Response)*

<table>
<thead>
<tr>
<th>Response Category</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable</td>
<td>26</td>
<td>100</td>
</tr>
<tr>
<td><strong>Major Response (MR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Pure Clinical</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td><strong>Total Major Response</strong></td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good (GPR)</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Minor</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total Partial Response</strong></td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td><strong>Stable Disease (SD)</strong></td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td><strong>Progressive Disease (PD)</strong></td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR + PR</td>
<td>18/26</td>
<td>69</td>
</tr>
<tr>
<td>MR + GPR</td>
<td>15/26</td>
<td>57</td>
</tr>
</tbody>
</table>


Gotlib et al, ASH 2010
Duration of Hematologic Responses

4/7 MCL patients (57%) achieved a major response, including 3 with ongoing incomplete remissions: ≥ 19 months (n = 2) and ≥ 32 months (n = 1)

<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of exposure</td>
<td>12.7 months (1.9-35.7)</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>26 months (12-36)</td>
</tr>
<tr>
<td>Kaplan-Meier estimate for duration of response</td>
<td>Not reached</td>
</tr>
</tbody>
</table>
Diagnostic Algorithm in SM
(Patient Selection for Drug Therapy)

Systemic Mastocytosis (SM) – by SM Criteria

No B & no C  C-Finding/s  2/3 B but no C

≥20% MC in bone marrow smears  AHNMD (WHO Criteria)  MC <20% and no AHNMD

MCL  (A)SM-AHNMD  ASM

ISM  SSM

TAKE HOME MEMORIZER:
B-Finding: High Burden of Mast Cells
C-Finding: C = Consider Cytoreduction

Valent et al., Blood 2010;116:5812-17; Valent et al., Leuk Res 2001;25:595
C-Findings

Findings resulting from organ destruction caused by local mast cell infiltration:

- Cytopenia(s)
- Liver involvement with ascites
- Huge osteolysis & pathologic fracture
- Malabsorption + hypalbuminemia
- Splenomegaly + hypersplenism

TAKE HOME MEMORIZER:

B-Finding: High Burden of Mast Cells
C-Finding: C = Consider Cytoreduction

Valent et al., Leuk Res 2001;25:595; Valent et al., Blood 2010;116:5812-17
Mast Cell Tryptase Levels in Healthy Subjects

- Normal basal Serum Total Tryptase Level
- Company: Range: 0-11.4 ng/ml
- **WW-ULN:** 10.0 to 15.0 ng/ml depending on Lab
- Our Lab (n≈300 healthy controls): 15.0 ng/ml
- What happens between 10.0 and 15.0 ng/ml?

→ Case Report
Case Report

- 47 year old female patient
- Referred because of elevated tryptase from Allergy Ambulatory
- Tryptase 12.3 ng/ml, repeat: 12.9 ng/ml
- Case History: arterial hypertension; and she was told to have an allergy against penicillin (´confirmed´ in the Allergy Ambulatory – but no test done)
- Allergy Tests all negative
Case Report

- Reaction to penicillin about 12 years ago uncertain – not confirmed by lab test, no typical clinical symptoms (shortness of breath & headache, no rash/hypotension)

- Doctors at the Allergy Laboratory had based the Diagnosis Allergy on the Serum Tryptase Level & the Reaction to Penicillin

- Is it justified? In several labs/studies such pts were excluded from ´normal population´!
## Cases 09/2009 – 06/2010

´Elevated´ Tryptase Levels*

<table>
<thead>
<tr>
<th>Case #</th>
<th>Tryptase</th>
<th>Age (yrs)</th>
<th>Gender (f/m)</th>
<th>BM</th>
<th>WBC (G/L)</th>
<th>Hb (g/dL)</th>
<th>PLT (G/L)</th>
<th>IgG/IgA</th>
<th>LDH (U/L)</th>
<th>Crea (mg/dL)</th>
<th>Known Allergy</th>
<th>LN</th>
<th>Splenitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>18.9</td>
<td>38</td>
<td>f</td>
<td>normal</td>
<td>7.7</td>
<td>12.5</td>
<td>275</td>
<td>normal</td>
<td>146</td>
<td>0.74</td>
<td>no</td>
<td>n.p.</td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td>29.1</td>
<td>71</td>
<td>m</td>
<td>normal</td>
<td>5.6</td>
<td>13.3</td>
<td>196</td>
<td>normal</td>
<td>205</td>
<td>0.78</td>
<td>Clindamycin?</td>
<td>n.p.</td>
<td></td>
</tr>
<tr>
<td>#3</td>
<td>18.4</td>
<td>61</td>
<td>f</td>
<td>normal</td>
<td>4.3</td>
<td>12.2</td>
<td>285</td>
<td>normal</td>
<td>84</td>
<td>1.1</td>
<td>no (Cipro??)</td>
<td>n.p.</td>
<td></td>
</tr>
<tr>
<td>#4</td>
<td>12.9</td>
<td>47</td>
<td>f</td>
<td>n.y.d.</td>
<td>6.8</td>
<td>12.9</td>
<td>158</td>
<td>normal</td>
<td>267</td>
<td>0.9</td>
<td>Penicillin?</td>
<td>n.p.</td>
<td></td>
</tr>
</tbody>
</table>

* In all 4 patients, the clinical symptoms leading to their referral to the Allergy Unit and then to our Department were atypical symptoms:

#1: Headache + GI symptoms in case history
#2: Examthema after Clindamycin (allergy possible – not confirmed)
#3: Suspected intolerance to Ciprofloxacin
#4: Atypical non-confirmed Reaction to Penicillin
Mastocytosis in the skin

Childhood

- Serum tryptase <20 ng/ml
  - other signs of systemic disease
    - yes
    - no
  - yes
  - CM
  - Mastocytosis in the skin
    - Monitoring until adolescence
    - Skin lesions regress and tryptase <20 ng/ml
      - CM
      - SM
    - Skin lesions persist and tryptase >20 ng/ml
      - Monitoring

Adults

- Serum tryptase ≥20 ng/ml
- Serum tryptase >100 ng/ml

Complete staging, apply SM-criteria

Multifocal MC infiltrates (≥ 15 MC/cluster by tryptase IHC) = major SM criterion

Morphology of MC

- >25% spindle shaped
- >5% but <25% spindle shaped
- >95% round MC = TROCI

SM

- Ask for minor SM criteria
  - At least one minor SM criterion
  - No minor SM criteria
    - CD117+/CD25-/CD34-
    - CD117+/CD25+/CD34-
    - CD117-
      - Ask for (atypical) mutations in KIT
        - Codon 816 KIT mutation
          - MMUS or MMAS*
          - Reactive MC hyperplasia
        - Mutations in codons other than 816
          - No mutation
            - SM
            - No MC neoplasm

Reconfirm the cell type by immunostaining
Grading of mediator-related symptoms

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = no symptoms</td>
<td>Prophylaxis**</td>
</tr>
<tr>
<td>1 = mild, infrequent therapy</td>
<td>Prophylaxis ± therapy</td>
</tr>
<tr>
<td>2 = moderate</td>
<td>Requires therapy, usually kept under control</td>
</tr>
<tr>
<td>3 = severe</td>
<td>Suboptimal control with daily combination therapy</td>
</tr>
<tr>
<td>4 = SAE***</td>
<td>Requires emergency therapy and hospitalization</td>
</tr>
</tbody>
</table>

*Most frequent symptoms to be graded: headache, nausea, systemic hypotension / anaphylaxis.*
**All patients with mastocytosis are advised to avoid precipitating factors and for most, prophylactic antihistamines (HR1 and HR2 antagonists) are recommended; ***the frequency of severe adverse events should be reported: A: <1/year; B: >1/year and <1/month; C: >1/month.

---

**Subdiagnostic BM infiltrates by tryptase IHC**

- Isolated MC infiltrate (tryptase +, ≥ 15 MC/cluster)
- Small sized MC infiltrate (tryptase +, < 15 MC/cluster)
- Isolated or small sized infiltrate + AHNMD

**Ask for minor SM criteria**

- ≥ 3 minor criteria
- < 3 minor criteria
- < 3 minor criteria
- ≥ 3 minor criteria

**SM**

- Repeat bm biopsy *
- Repeat bm biopsy after cytoreduction
- SM-AHNMD

**CM**

- Presence of mediator related symptoms
  - Yes
  - No

**MMAS**

- MMUS

**Ask for myelomastocytic leukemia or another tryptase+ myeloid neoplasm**

---

*E*
Response Criteria in ASM/MCL

I: **Major Response:**
Complete resolution of at least one (= one or more) C-Finding(s) 
and no progression in other C-Findings
  a) Complete remission = with disappearance of mast cell infiltrates in affected organs, decrease of serum tryptase levels to < 20 ng/ml, and disappearance of SM-associated organomegaly
  b) Incomplete remission = with decrease in mast cell infiltrates in affected organs and/or substantial decrease of serum tryptase level and/or visible regression of organomegaly
  c) Pure clinical response = without decrease in mast cell infiltrates, without decrease in tryptase levels, and without regression of organomegaly

II: **Partial Response:**
Incomplete regression of one or more C-Finding(s)* without complete regression and without progress in other C-Findings
  a) Good partial response: > 50% regression
  b) Minor response: ≤ 50% regression

III: **No Response:**
C-Finding(s) are persistent or are progressive**
  a) Stable disease: C-Finding-parameters show constant range
  b) Progressive disease: one or more C-Finding(s) show progression

* with or without decrease in mast cell infiltrates, serum tryptase levels, and organomegaly
** in case of progressive C-Findings and documented response in other C-Finding(s), the final diagnosis is still: progressive disease
Grading of constitutional and mediator-related symptoms in patients with SM ($\text{SM}_\text{SY}$)

<table>
<thead>
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<tr>
<td>0 = no symptoms</td>
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<td>requires emergency therapy and hospitalization</td>
</tr>
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</table>

Most frequent symptoms to be graded:
headache, nausea, systemic hypotension / anaphylaxis

*The frequency of severe adverse events should also be reported:

A: $<1$/year; B: $>1$/year and $<1$/month; C: $>1$/month
<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Regression (CR)</td>
<td>all symptoms completely resolved and not observed again during 12 months after therapy</td>
</tr>
<tr>
<td></td>
<td>- Continuous CR (CCR) no further symptoms after 2 years**</td>
</tr>
<tr>
<td>Major Regression (MR)</td>
<td>improvement of symptoms by &gt;50% or/and decrease in frequency of severe (grade 4) events from B to A or from C to B</td>
</tr>
<tr>
<td>Partial Regression (PR)</td>
<td>improvement to 10-50% or/and minor decrease in frequency of severe events (less than defined for the MR group – see above)</td>
</tr>
<tr>
<td>No Regression (NR)</td>
<td>&lt;10% improvement and no decrease in frequency of severe events</td>
</tr>
</tbody>
</table>
RECOMMENDATIONS:

- SCREEN FOR & STAGE THE NON-MAST CELL NEOPLASM AS IF NO SM WAS DIAGNOSED
- APPLY WHO CRITERIA!
- SCREEN FOR (POTENTIAL) DRUG TARGETS
- ASK WHETHER KIT D816V IS EXPRESSED IN NEOPLASTIC (SM- AND AHNMD-) CELLS
- DETERMINE THE SUBTYPE OF THE SM-COMPONENT (e.g. ISM-AHNMD versus ASM-AHNMD)
- REFER THE PATIENT TO A HEMATOLOGY CENTER
Recommended Diagnostic Procedures in suspected SM-AHNMD

- Eosinophils > 1500 +/- specific organopathy
- Basophils, left shift
- Dysplasia, Monocytosis in pb > 1000 Immature monocytes in bm
- Dysplasia, peripheral Cytopenia Blasts < 20%
- Blasts ≥ 20%
- FIP1L1-PDGFRα and signs of HES/CEL
- bcr/abl, t(9;22)
- inv16

CELSHES CMLCMMLMDSAML
HES & CEL + / - SM by WHO criteria

A: Start → Algorithm:

a) SM (SM criteria fulfilled) + eosinophilia (eosinophils >1,500/µL) = SM-eo (prediagnostic !)

b) HES or CEL (WHO criteria fulfilled) + MC ↑

B: Final Diagnosis (BY CRITERIA):

- SM (eo ↑) (define SM subvariant !) rare
- SM-HES (define SM subvariant !) extremely rare
- SM-CEL (define SM subvariant !) very rare
- HES rare
- CEL rare