Clinicopathologic and Molecular Correlates of Organ Damage across the Spectrum of Advanced Systemic Mastocytosis

Emily C. Liang[1], Cecelia Perkins[2], Rong Lu[3], Hongliang Shi[4], Saša Dimitrijević[5], Gerard Hoehn[4], Justin Abuel[2], Cheryl Langford[2], Parveen Abidi[2], Lenn Fechter[2], William Shomali[2], Jason Gotlib[2]

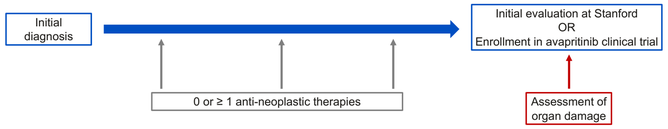
[1]Department of Medicine, [2]Division of Hematology, Stanford Cancer Institute, [3]Quantitative Sciences Unit, Stanford University School of Medicine, Stanford, CA, [4]Blueprints Medicine Corporation, Cambridge, MA, [5]Blueprints Medicine Corporation, Zug, Switzerland

Background

- Systemic mastocytosis (SM) is characterized by the accumulation of neoplastic mast cells in various organs.
- Advanced SM (AdvSM) comprises 3 subtypes: aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).
- Patients (pts) with AdvSM often exhibit hematologic and/or non-hematologic organ damage due to neoplastic mast cell infiltration.
- The definition of hematologic and non-hematologic organ damage has evolved from World Health Organization (WHO) C-findings, to organ damage criteria specified by the International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG).
- More recently, modified IWG (mIWG) criteria have been used to define eligible organ damage in trials of AdvSM.
- The presenting patterns of organ damage across the AdvSM subtypes have not been well characterized.

Objectives and Study Cohort

- **Objectives:**
  1) To describe the distribution of organ damage in AdvSM pts at initial presentation or at time of trial enrollment using WHO, IWG, and mIWG criteria
  2) To evaluate clinicopathologic and molecular correlates of organ damage
- **Study design:** Observational study of 68 AdvSM pts from Stanford MPN registry and 176 pts from phase I EXPLORER and phase II PATHFINDER studies of avapritinib in AdvSM
- **Statistical methods:** Comparisons between continuous and categorial variables were performed using the Wilcoxon rank sum test and the Fisher's exact test, respectively. The Benjamini and Hochberg method was used to control the false discovery rate in multiple comparisons.



Demographics of study cohort

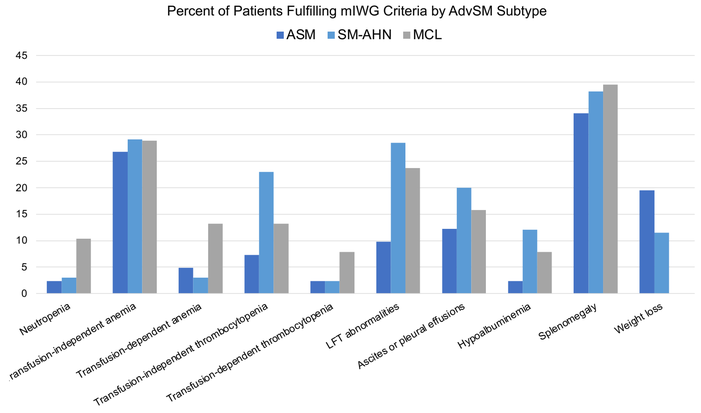
- Patients enrolled in the avapritinib studies had a longer median duration between diagnosis and initial presentation or study enrollment than patients from the Stanford MPN registry (11 months vs. 3 months, p < 0.001). They were more likely to have been previously treated with midostaurin (p < 0.001).

Characteristic	ASM n = 41	SM-AHN n = 165	MCL n = 38	Full cohort n = 244
Male (%)	17 (15)	105 (64)	24 (63)	146 (60)
Age at initial presentation or study enrollment, median, years (range)	64 (30-77)	69 (24-88)	60 (26-92)	68 (24-88)
Time between diagnosis and initial presentation or study enrollment, median, months (range)	19 (0-254)	7 (0-638)	14 (0-1440)	8 (0-1440)
Number of prior anti-neoplastic therapies, median (range)	1 (0-6)	1 (0-6)	1 (0-4)	1 (0-6)
Number of mIWG organ damage findings, median (range)				
Hematologic	0 (0-2)	0 (0-2)	0 (0-3)	0 (0-3)
Non-hematologic	1 (0-3)	1 (0-4)	1 (0-4)	1 (0-4)
Total	1 (0-4)	2 (0-6)	2 (1-6)	1 (0-6)

Results

Comparison of AdvSM subtypes

- Pts with MCL had the highest transfusion requirement: 13% required RBC transfusions, and 8% of pts required platelet transfusions.
- SM-AHN pts had the highest median alkaline phosphatase (ALP) (214 U/L, range 33-1680), while pts with MCL had the largest median liver (2860 cm^3, range 1370-4140) and spleen (1120 cm^3, range 258-2270) volumes by imaging.
- Pts with SM-AHN fulfilled the WHO thrombocytopenia criterion more frequently than MCL and ASM pts, and more WHO hematologic (p = 0.02) and IWG non-hematologic (p = 0.008) criteria than ASM pts.
- Among the two largest SM-AHN subtypes, pts with SM-CMML (n = 72) had a lower ANC (p = 0.02) and tryptase levels (p = 0.04) than pts with MDS/MPN-U.
- In multivariate analyses using random forest models comparing SM-AHN to ASM/MCL, SM-AHN pts had higher ANC, absolute monocyte count, and presence of S/A/R mutations. ASM/MCL pts had higher tryptase levels and BM MC burden.



Prior therapy

- Pts who received ≥1 prior anti-neoplastic therapy (compared to none) had higher tryptase levels (p = 0.02) and bone marrow (BM) MC burden (p = 0.03), lower ALP (p = 0.04), and higher likelihood of meeting WHO malabsorption criteria (p = 0.03).
- Compared to midostaurin-naïve pts, those who had received midostaurin had a higher BM MC burden (p = 0.045), but less frequently met the mIWG splenomegaly criterion (p = 0.03) and met fewer WHO non-hematologic criteria (p < 0.001).

Mutation profile

- Compared to pts with *KIT* D816V only, pts who also had ≥1 *SRSF2*, *ASXL1*, or *RUNX1* mutations had a lower median hemoglobin (p = 0.02), platelet count (p = 0.02), and higher direct bilirubin (p = 0.02), ALP (p = 0.03), and spleen volume (p = 0.06). They exhibited more WHO-defined cytopenias (p = 0.007) and were more likely to fulfill the WHO hypersplenism criterion (p = 0.03).
- Compared to pts with *KIT* D816V only, pts who had ≥2 additional myeloid gene mutations exhibited more WHO-defined cytopenias (p = 0.03) and were more likely to fulfill the WHO hypersplenism criterion (p = 0.04).

Correlation matrices showing strength of association between organ damage components by AdvSM subtype

Hematologic organ damage

- In all 3 subtypes, Hb and platelet count were inversely correlated with the number of hematologic, non-hematologic, and total organ damage findings.
- ANC and the number of hematologic, non-hematologic, and total organ damage findings were inversely correlated in ASM and MCL, and positively correlated in SM-AHN.

Non-hematologic organ damage

- Direct bilirubin and ALP were positively correlated with spleen size, liver size, and number of organ damage findings, while albumin was inversely correlated with these findings.
- In ASM and SM-AHN, serum tryptase and BM MC burden were positively correlated with spleen size, liver size, and number of hematologic, non-hematologic, and total organ damage findings.

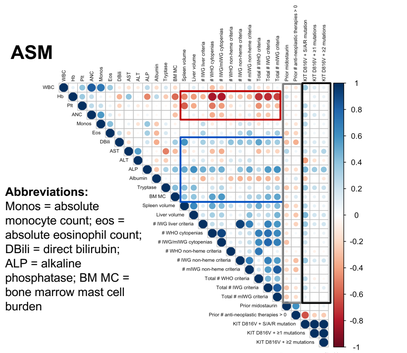
Prior therapy

- Prior treatment with midostaurin or at least 1 anti-neoplastic therapy was associated with fewer number of non-hematologic organ damage findings.

Mutation profile

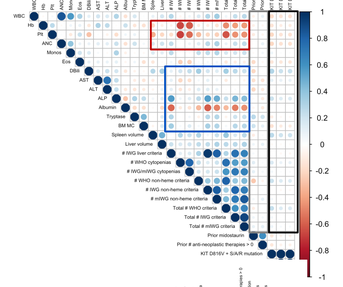
- Presence of *SRSF2*, *ASXL1*, or *RUNX1* mutations and ≥1-2 additional myeloid gene mutations were associated with WHO-defined cytopenias.
- Presence of these mutations and the number of non-hematologic organ damage findings were positively correlated in ASM and SM-AHN, and inversely correlated in MCL.

ASM

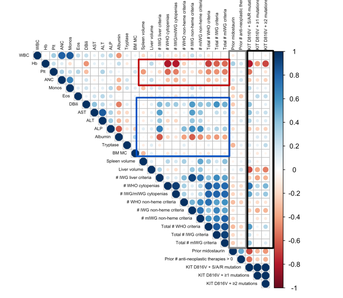


Abbreviations:
Monos = absolute monocyte count; eos = absolute eosinophil count; DBili = direct bilirubin; ALP = alkaline phosphatase; BM MC = bone marrow mast cell burden

SM-AHN



MCL



Conclusions

- We provide a comprehensive evaluation of the patterns of WHO and IWG/mIWG-defined organ damage across the spectrum of AdvSM.
- Patterns of organ damage reflect disease subtype, prior therapy, and mutation profile beyond *KIT* D816V.
- Receipt of anti-neoplastic therapy (especially midostaurin) was generally associated with less non-hematologic organ damage, but with higher BM MC burden, suggesting a possible discordant impact on organ involvement.
- In SM-AHN, additional myeloid mutations are associated with greater organ damage, including cytopenias and hypersplenism. This may in part reflect the presence of both the SM and AHN components since a multi-mutated state is common in SM-AHN
- These data can help inform the clinical heterogeneity of AdvSM pts who are being evaluated for clinical trials, which currently require one or more organ damage findings defined by the WHO, IWG, or mIWG criteria.

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