Evaluation of Survival Among Patients With Indolent Systemic Mastocytosis: A Population-Level Retrospective Cohort Analysis Using Healthcare Claims Dataset

Sudipto Mukherjee¹, Douglas J. Cattie², Daniel Shaheen², Dakota Powell², Teresa Green²

¹Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; ²Blueprint Medicines Corporation, Cambridge, MA, USA
Background and Objective

Background

• Systemic mastocytosis (SM) is a rare, heterogenous, clonal mast cell disease driven by the KIT D816V mutation in up to 95% of cases\textsuperscript{1-3}

• Indolent systemic mastocytosis (ISM) is the most common subtype, characterized by a more chronic clinical course associated with a significant symptom burden that may worsen over time, poor quality of life, and the potential for life-threatening anaphylaxis\textsuperscript{4,5}

• Patients with more disease risk factors may demonstrate higher symptom burden and may have increased rates of disease progression and mortality\textsuperscript{6}

Objective

• The objective of this analysis was to evaluate overall survival (OS) in patients with ISM to build upon the existing literature and further establish the impact of ISM on survival

New Evidence Suggests Diminished Survival in ISM

**2009**


- Evaluated N = 159 patients with ISM
- Single-center study (Mayo Clinic)
- Median follow-up 1.7 years post-diagnosis

**Conclusion:**

*Survival of ISM population not significantly different from expected US survival*

**2019**


- Evaluated N = 1,006 patients with ISM
- Multi-center study (ECNM registry)
- Median follow-up 3.4 years

**Conclusion:**

*Survival of ISM patients was diminished versus cutaneous mastocytosis patients*

**2020**


- Evaluated N = 393 patients with ISM
- National population-based cohort study, Danish National Health Registries
- ISM patient survival was compared to a matched non-ISM cohort
- Median follow-up 9 years

**Conclusion:**

*Mortality was increased among ISM populations versus non-ISM patients, with hazard ratio of 1.53 – 2.59*

---

AHD, systemic mastocytosis with associated hematologic disorders; ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; ECNM, European Competence Network on Mastocytosis; ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; OS, overall survival; SM, systemic mastocytosis.
Previous Studies have Explored the Risk of Progression from ISM to Advanced SM

- In a two-year interval, 3.9% of ISM patients were observed to progress from indolent SM to advanced SM.
- Using a discrete-time Markov modeling approach, modeled the cumulative risk of disease progression from ISM to Advanced SM across a patient's total disease course.
- Model is based on empirical fixed-interval rates of survival and progression documented in literature.
- Estimate cumulative risk of progression from indolent SM to advanced SM to be 18.0% ± 3.1% S.D.


AdvSM, advanced SM; TKI, tyrosine kinase inhibitor.

Study Design and Methodology

~320 million patients in US Healthcare Claims Dataset

~25,000 patients with some evidence of SM

Any of the following criteria:
• Patient required 2+ SM ICD-10 diagnosis codes ≥ 30 days apart
• Patient received SM ICD-10 diagnosis code after a bone marrow biopsy
• Patient received a therapy specific to SM (SM-directed TKI, cladribine, interferons, cromolyn sodium, omalizumab)

AND
Patient required to have >1y of closed claims data (i.e. comprehensive of all medical & pharmacy claims)

AND
Evidence of ISM precedes any evidence of advanced SM

8332 suspected ISM patients with sufficient claims depth and follow-up

CCI, Charlson Comorbidity Index; ICD-10, International Classification of Diseases, Tenth Revision.

Additional Methodological Detail:
• Study period: 2015 – 2022
• Analysis anchored to the first observed ICD-10 diagnosis code for SM
  – Progression to advanced SM was inferred if a patient generated a subsequent code specific to mast cell leukemia (MCL), aggressive SM, or an associated hematologic neoplasm (AHN)
• Mortality information available within claims dataset, and inferred if a patient did not generate any medical or pharmacy claims for 12 or more consecutive months
• Three independent non-SM control groups established through stratified sampling approach, matched by sex, age, CCI, payer status, and race/ethnicity of the ISM population
### Patient Characteristics for ISM and Control Groups Well Matched

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2421 (29.1)</td>
<td>569 (28.5)</td>
<td>577 (28.9)</td>
<td>582 (29.1)</td>
</tr>
<tr>
<td>Female</td>
<td>5911 (70.9)</td>
<td>1431 (71.6)</td>
<td>1423 (71.2)</td>
<td>1418 (70.9)</td>
</tr>
<tr>
<td><strong>Age in years, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–35</td>
<td>2314 (27.8)</td>
<td>559 (28.0)</td>
<td>547 (27.4)</td>
<td>550 (27.5)</td>
</tr>
<tr>
<td>36–48</td>
<td>2085 (25.0)</td>
<td>494 (24.7)</td>
<td>496 (24.8)</td>
<td>493 (24.7)</td>
</tr>
<tr>
<td>49–60</td>
<td>2016 (24.2)</td>
<td>488 (24.4)</td>
<td>483 (24.2)</td>
<td>486 (24.3)</td>
</tr>
<tr>
<td>61+</td>
<td>1917 (23.0)</td>
<td>459 (23.0)</td>
<td>474 (23.7)</td>
<td>471 (23.6)</td>
</tr>
<tr>
<td><strong>CCI, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1666 (20.0)</td>
<td>396 (19.8)</td>
<td>405 (20.3)</td>
<td>387 (19.4)</td>
</tr>
<tr>
<td>1</td>
<td>1592 (19.1)</td>
<td>381 (19.1)</td>
<td>380 (19.0)</td>
<td>385 (19.3)</td>
</tr>
<tr>
<td>2–3</td>
<td>2600 (31.2)</td>
<td>633 (31.7)</td>
<td>624 (31.2)</td>
<td>628 (31.4)</td>
</tr>
<tr>
<td>4+</td>
<td>2474 (29.7)</td>
<td>590 (29.5)</td>
<td>591 (29.6)</td>
<td>600 (30.0)</td>
</tr>
<tr>
<td><strong>Payer, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>6063 (72.8)</td>
<td>1455 (72.8)</td>
<td>1452 (72.6)</td>
<td>1459 (73.0)</td>
</tr>
<tr>
<td>Medicare</td>
<td>908 (10.9)</td>
<td>220 (11.0)</td>
<td>228 (11.4)</td>
<td>217 (10.9)</td>
</tr>
<tr>
<td>Medicare Advantage</td>
<td>485 (5.8)</td>
<td>113 (5.7)</td>
<td>107 (5.4)</td>
<td>114 (5.7)</td>
</tr>
<tr>
<td>Managed Medicaid</td>
<td>538 (6.5)</td>
<td>129 (6.5)</td>
<td>130 (6.5)</td>
<td>128 (6.4)</td>
</tr>
<tr>
<td>Other</td>
<td>338 (4.1)</td>
<td>83 (4.2)</td>
<td>83 (4.2)</td>
<td>82 (4.1)</td>
</tr>
<tr>
<td><strong>Race/ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic or Latino</td>
<td>3613 (43.4)</td>
<td>869 (43.5)</td>
<td>874 (43.7)</td>
<td>865 (43.3)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>387 (4.6)</td>
<td>95 (4.8)</td>
<td>90 (4.5)</td>
<td>95 (4.8)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>226 (2.7)</td>
<td>53 (2.7)</td>
<td>52 (2.6)</td>
<td>55 (2.8)</td>
</tr>
<tr>
<td>Unknown/other</td>
<td>4106 (49.3)</td>
<td>983 (49.2)</td>
<td>984 (49.2)</td>
<td>985 (49.3)</td>
</tr>
</tbody>
</table>

*Note: Race and ethnicity were matched between cohorts; however, this information was only available for approximately 50% of the patients.*

ISM, indolent systemic mastocytosis.

Data presented as n (%).

American Society of Hematology
Overall Survival is Consistent Among Non-SM Control Cohorts

- Three independent samplings of non-SM control cohorts produced patient populations that were consistent in their survival ($P = 0.7950$)

- As all 3 cohorts had similar rates of survival, patients with ISM in this analysis were compared to control cohort 1

Note: To assess the face validity of this analytic approach, survival for patients with aggressive SM was compared to a control cohort, producing results in line with existing literature ($P < 0.0001$, log-rank HR of 6.64, 95% CI 3.56–12.39)

Note the truncated Y-axis in the indicated figures

ISM, indolent systemic mastocytosis; SM, systemic mastocytosis
Overall Survival in Patients With ISM is Diminished Compared to Matched Non-SM Patients

- Patients with ISM had a statistically significant difference in OS compared to the matched non-SM cohorts ($P < 0.0001^*$, with a log-rank HR of 1.70, 95% CI 1.39–2.10)

- Excess mortality was noted among ISM patients without evidence of disease progression compared to matched non-SM cohorts ($P = 0.0005$, with a log-rank HR of 1.53, 95% CI 1.23 – 1.90)

- Patients with evidence of progression to AdvSM had worse survival ($P < 0.0001^*$, log-rank HR of 3.87, 95% CI 2.58 – 5.79)

*Nominal P-value
HR, hazard ratio.

$^*$ Progression to advanced SM was inferred based on a subsequent ICD-10 diagnosis code for aggressive SM, mast cell leukemia, or an associated hematologic malignancy
Health Resource Utilization Among ISM Patients Shows Disease Burden

- The ISM cohort presented to the ER 0.70 times per year, compared to 0.31 times per year for the combined non-ISM control cohorts, based on the sum of ER visits observed across the cumulative cohort observation period.
- Patients with ISM who died during the study interval had the highest frequency of ER visits at a rate of 1.09 visits per year.

Note: The COVID pandemic caused reductions in claims volume and was an exogenous source of excess mortality. This may result in an underestimation of ED use and comorbidities (captured in CCI) and attenuated survival across cohorts.
Conclusions

• This is the first and largest population-level claims analysis of OS in the ISM population in the US.
• The results of this analysis demonstrated a statistically significant decrease in survival among patients with ISM compared with matched non-SM cohorts (P < 0.0001), consistent with emerging evidence from large national disease registries.
• This decrease in survival was observed in both ISM patients who showed progression to AdvSM and those who did not. Notably patients with ISM visited the emergency department at twice the rate of control cohorts.
• These data support emerging evidence that ISM comprises a wide phenotypic spectrum with certain patients being at a greater risk of progression to advanced disease and increased mortality, and who may benefit from earlier therapeutic intervention.

Acute, severe symptoms of ISM, in addition to progression risk, may contribute to the excess mortality seen among patients with ISM and warrant focused research to identify specific patient characteristics or disease features that confer a higher risk of mortality.
Acknowledgments

• Medical writing and editorial support were provided by Kimberly Dent-Ferguson, MBS, MPH, of Red Nucleus, and funded by Blueprint Medicines Corporation