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William Carey University College of Osteopathic Medicine

SIDNEY BROWN, OMS III, DILLON FOUNTAIN, OMS III, AND SKYLAR MAI, DDS

Comparative Safety of Avapritinib, Midostaurin, and Cladribine in Systemic Mastocytosis: A Meta-Analysis

Introduction

Systemic mastocytosis (SM) is a rare clonal mast cell disorder characterized by heterogeneous clinical presentations and varying disease severity. While several pharmacologic treatments are approved or in use for advanced forms of SM, including avapritinib, midostaurin, and cladribine, each drug carries a distinct safety profile. Given the chronic nature of treatment and the potential for serious adverse events (AEs), understanding the comparative safety of these agents is critical to guide therapy selection and patient counseling.

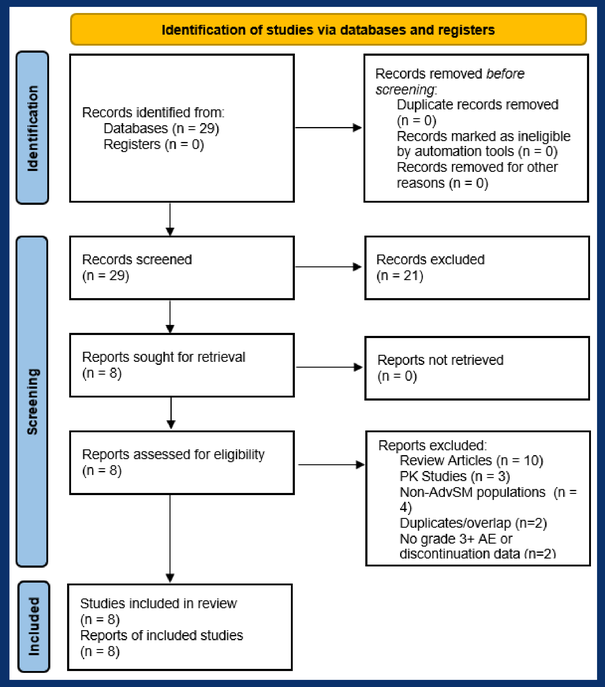
Objective

To evaluate and compare the safety profiles of avapritinib, midostaurin, and cladribine in adult patients with systemic mastocytosis.

Methodology

1. Registered with Prospero (ID # CRD420251061250)
2. Search: PubMed (to June 2025) using advanced systemic mastocytosis, avapritinib, midostaurin, cladribine.
3. Screening: 29 records screened → 21 excluded → 8 included (n = 462).
4. Data extracted: study design, population, sample size, grade 3+ hematologic adverse events, treatment discontinuations.
5. Risk of bias: Cochrane RoB (trials) and ROBINS-I (observational).
6. Analysis: Analysis: Random-effects meta-analysis was used to pool event rates, with results reported as proportions and 95% confidence intervals.

PRISMA Flowchart



Safety Outcomes

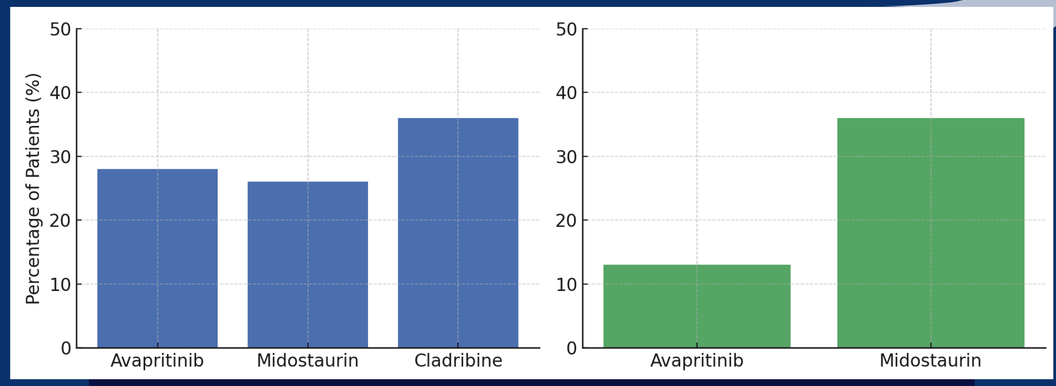


Figure 1. (A): Grade ≥ 3 hematologic adverse events by drug — Avapritinib: 28.0%, Midostaurin: 26.0%, Cladribine: 36.0% (single study).
(B): Treatment discontinuations (%) — Avapritinib: 13.0%, Midostaurin: 36.0%, Cladribine: Not reported (<5% estimated).

Results

Drug	Typical AE Type	Risk of Bias
Avapritinib	Thrombocytopenia	Moderate
Midostaurin	Anemia, GI upset	Moderate–High
Cladribine	Myeloid cytopenia	High

Table 1. Risk of bias ranged from moderate to high, reflecting mostly open-label, single-arm designs with variable follow-up durations. The most common Grade 3+ adverse events were hematologic cytopenias indicating that bone marrow suppression is the predominant toxicity concern across all therapies.

Conclusion

Avapritinib → Moderate rate of grade ≥ 3 hematologic AEs (~28%) but comparatively few discontinuations (~13%); toxicity is generally manageable with monitoring and dose adjustment.
Midostaurin → Similar hematologic AE rate (~26%) but markedly higher discontinuations (~36%), largely due to gastrointestinal intolerance and treatment fatigue.
Cladribine → Limited data (n = 22); cytopenias common (~36%) yet few discontinuations reported.

When selecting therapy for AdvSM, providers should balance cytopenic risk (higher with avapritinib and cladribine) against GI and discontinuation rates (higher with midostaurin). Real-world data favor avapritinib for sustained tolerability. Most studies enrolled patients with AdvSM (ASM, SM-AHN, MCL); results may not generalize to indolent forms. Avapritinib's high KIT D816V selectivity may reduce off-target kinase inhibition, explaining its lower GI discontinuations but higher cytopenia rates.

References

The authors report no relevant financial relationships or conflicts of interest.