Treatment of Cutaneous Mastocytosis: A Systematic Review

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Abstract

Cutaneous mastocytosis (CM) is a rare disorder characterized by cutaneous accumulation of mast cells, leading to significant symptom burden. Due to its rarity, the evidence for its management is fragmented. This systematic review aims to synthesize the available evidence on CM treatments and their effects on clinical outcomes. Following PRISMA guidelines, a comprehensive search of PubMed, Scopus, and Cochrane was conducted from database inception to January 15, 2025, using a predefined search strategy with relevant keywords and MeSH terms. Ten studies (N=333 total), spanning a publication period from 2003 to 2023, examining a range of interventions were included. Topical corticosteroids and pimecrolimus can improve or hasten lesion regression in children. Phototherapy with UVA1 showed efficacy in alleviating symptoms in adults with MPCM, while NB-UVB was reported in a small case series to yield dramatic lesion and pruritus improvement. For severe refractory symptoms, omalizumab demonstrated a response in 10/11 (90.9% overall response) patients in CM-subgroup for controlling mediator-related symptoms, while cladribine showed response in 6/6 (100%) patients in a small CM subgroup but with significant toxicity. No severe treatment-related adverse events were reported with topical treatments or phototherapy. Risk of bias was generally high, with two comparative studies rated as having moderate risk. Our review showed that a range of therapies, from topical agents to systemic therapies, can provide benefit in CM. However, treatment should be individualized based on patient's disease severity, age, and symptom profile. Larger controlled trials are needed to establish a stronger evidence base and to better understand the efficacy of these interventions.

Keywords: *cutaneous mastocytosis, mastocytosis, outcome, systematic review, treatment, urticaria pigmentosa*

1. Introduction

Cutaneous mastocytosis (CM) is a subset of mast cell disorders characterized by abnormal mast cell infiltration limited to the skin, and can be subclassified into maculopapular cutaneous mastocytosis (MPCM), historically known as urticaria pigmentosa (UP), mastocytoma of the skin, and diffuse CM (DCM) (Brockow et al., 2024). In children, CM usually follows a benign course, with gradual regression of lesions and symptoms by adolescence in the majority of cases (Sharquie & Alhyali, 2022). In contrast, adult-onset CM is often associated with systemic involvement, and truly isolated cutaneous disease is rarer in adults. Consequently, studies of adult populations with CM frequently include patients with systemic mastocytosis (SM), making the effects of interventions on pure CM difficult to isolate (Brockow, 2014). The clinical manifestations of CM result from mast cell mediator release including pruritus, flushing, urticaria, dermographism, and blistering, which can significantly impact quality of life (Hartmann et al., 2016). The diagnosis of CM is based on the typical morphology of skin lesions, the presence of Darier's sign and an increased number of mast cells in biopsy sections of the lesion. In unclear cases, the detection of a *KIT* mutation in skin lesions may confirm the diagnosis of CM (Hartmann et al., 2016). Therapies for CM are often focused on symptomatic control and improvement of skin lesions (Le et al., 2017). However, due to disease rarity, the evidence is scattered and largely based on expert opinion rather than on evidence obtained from robust trials (Siebenhaar et al., 2014). This systematic review aims to synthesize the available evidence on CM treatments and assess their reported outcomes with the goal of informing clinical practice and identifying areas for future research.

2. Objectives

1) To synthesize evidence on CM treatments and evaluate their effects on patient's clinical outcomes, including symptom relief, lesion reduction, quality of life, and adverse effects.

2) To compare the efficacy and safety profiles across topical therapies, phototherapy, and systemic treatment options, and to propose an evidence-informed stepwise approach to CM management based on the strength and limitations of the available evidence.

3. Materials and Methods

This systematic review was conducted in accordance with the PRISMA 2020 guidelines to ensure transparency and completeness (Page et al., 2021). Given the rarity of CM, we anticipated that RCTs would be scarce; therefore, we designed this as a systematic narrative review. This review was not registered in PROSPERO due to multiple refinements during the protocol development phase to address the complexities of synthesizing evidence in this rare disease. Nevertheless, all eligibility criteria, search strategies, data extraction methods, and analysis plans were predefined and documented before we extracted the data.

3.1 Eligibility Criteria

The eligibility criteria were established using PICOs framework, with population (P): patient at any age diagnosed with CM, including all recognized subtypes. Studies including mixed populations with both CM and SM patients were included only if outcome data specific to the CM subgroup were extractable from the publication. For such studies, we established a rule that only data from the CM subset would be included in the primary analysis to avoid bias or dilute of the estimated treatment effects of the cutaneous only disease. Intervention (I): any therapeutic interventions aimed at managing CM. Comparator (C): any or none. Outcomes (O): studies had to report on any clinically relevant outcomes, such as symptom relief, lesion improvement, quality of life, or any adverse effects associated with treatment. Study design (S) were any primary research studies, including randomized controlled trials (RCTs), non-randomized controlled trials (non-RCTs), cohort studies, observational studies, and case series (n>5). Languages and Publication date: published in English within the publication period from 2000 to 2025 to capture more recent treatment and evidence, given advancements in CM treatment options in the past two decades. Case series were included due to the rarity of CM, which limits the availability of higher-level evidence. Studies were excluded if they were non-human, review articles, lack of extractable CM-specific outcome data, and non-therapeutic focused. Case reports and small case series (n<5) were excluded from the main synthesis but were summarized in supplementary table S1 to provide a comprehensive overview of the treatment landscape and were briefly mentioned in the discussion section for additional context.

3.2 Search Strategy

A comprehensive literature search was performed on January 15, 2025, across three databases including PubMed, Scopus, and Cochrane Library. All studies from database inception to January 15, 2025, were considered, without restricting to specific filters. The search strategy combined Medical Subject Headings (MeSH) terms and relevant keywords related to three core concepts: (1) Cutaneous mastocytosis (e.g., “mastocytosis, cutaneous”, “skin, mastocytosis”, “urticaria pigmentosa”), (2) Intervention (e.g., “treatment,” “therapy,” “drug therapy,”), and (3) Clinical outcomes (e.g., “clinical outcomes”, “symptom relief”, “quality of life”, “outcomes”). Boolean string (AND/OR) were used to combine key terms, while truncation was used to avoid spelling variation and to optimize sensitivity. Search strategy: 1 AND 2 AND 3. The full search strings for each database are provided in Appendix 1.

3.3 Study Selection

Search results were imported into Zotero for deduplication. Then the data were imported into Rayyan tool, which automatically imports the title, author(s), abstract, year of publication and journal, volume and issue information for screening. A two-step selection process was then conducted independently by two reviewers. First step: both reviewers independently screened titles and abstracts according to the pre-specified criteria to exclude irrelevant articles. During that process any other duplicate records that were found will also be removed manually. Second step: full-text articles of potentially eligible studies were retrieved and independently assessed for inclusion by both reviewers. Studies were excluded when access to full text is not available or did not meet the eligibility criteria. For studies including mixed populations, we applied our pre-

specified rule that they were included only if the outcome data specific to the CM subgroup could be extracted. At both stages, any disagreements between both reviewers were resolved through discussion and consensus. A third reviewer was not required as all disagreements were successfully resolved through discussion. The selection process and reasons for exclusion at the full text stage are documented in Figure 1.

3.4 Data Extraction and Synthesis

For all included studies, data were independently extracted by both reviewers into a customized data sheet developed specifically for this review using Microsoft Excel. Data items to be extracted included details on study design, population, CM subtype, intervention details, outcomes, and key findings. Outcomes were grouped into domains such as symptom relief (pruritus, flushing, or any other local mast cell mediator symptoms), lesion improvement (complete or partial resolution of skin lesions, improvement in lesion appearance and pigmentation), quality of life (measured by validated tools or patient reports), and adverse effects. Any discrepancies in data extraction were resolved through consensus discussion.

3.5 Risk Bias of Assessment

The methodological quality and risk of bias were assessed using tools developed and recommended by the Cochrane Collaboration, which represent the current standard for systematic reviews of healthcare interventions. For non-randomized studies of interventions (NRSIs) including cohort studies, and non-randomized trials, the Cochrane Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) tool was used. The ROBINS-I tool is the current methodological standard for such studies as it can rigorously appraise domains such as confounding, participant selection, classification of intervention, deviations from intended interventions, missing data, outcome measurement, selection of reported results, and provide overall risk assessments of "Low", "Moderate", "Serious", or "Critical" (Sterne et al., 2016). On the other hand, for studies whose primary purpose was descriptive reporting on a series of patients (case series), they were appraised with the use of Joanna Briggs Institute (JBI) Critical Appraisal Checklist to assess 10 items covering inclusion criteria, standardization of condition measurement, validity of methods, completeness of inclusion, demographics, clinical information, outcomes reporting, and statistical analysis (Munn et al., 2020). Two reviewers independently assessed the risk of bias for each study, followed by comparison and discussion. Any disagreements were resolved through discussion and consensus by the two reviewers. To facilitate a unified graphical representation of the methodological quality of all included studies, the responses from the JBI checklist were mapped onto a risk of bias framework consistent with ROBINS-I.

3.6 Data Synthesis

Given the heterogeneity of study designs and outcomes, a meta-analysis was not feasible. Instead, we conducted a narrative synthesis, structuring the results by intervention type and outcome domain. To standardize outcome reporting across studies, we extracted specific outcome metrics where available, including pruritus Visual Analog Scale (VAS), Dermatology Life Quality Index (DLQI), SCORMA index, lesion counts, and investigator-assessed response categories. These extracted metrics are presented for each study in Table1, along with reported time points of assessment where available. However, not all studies used these standardized measures, and this heterogeneity is acknowledged as limitation. Because outcomes were variably reported, to allow some uniformity, we classified each study's primary outcome direction as positive (improvement in CM lesion/symptoms), no change, or negative (worsening or significant adverse effects). This classification facilitated the visual summary presented in the harvest plot (Figure 4).

3.7 Certainty of Evidence

The overall certainty of evidence was assessed narratively by considering the core GRADE domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Due to the absence of randomized controlled trials and the predominantly observation study designs, no formal summary of finding table was constructed. Instead, GRADE assessments were applied qualitatively to judge the certainty of evidence, which were reported narratively in the Discussion.

4. Results

4.1 Study Selection and Characteristics

A total of 336 records were identified through 3 differences database: PubMed (n=198), Scopus (n=124), and Cochrane Central Register of Controlled Trials (n=14). Among them, 41 duplicate records were automatically removed using Zotero, and 7 others were identified using Rayyan software. After the removal of those 48 duplicate records, this left us with 288 records for title/abstract screening. During the initial screening, 207 records were deemed as irrelevant and were excluded based on our inclusion and exclusion criteria. The remaining 81 full-text articles were retrieved for detailed evaluation to assess their eligibility, with one article inaccessible despite exhaustive efforts. Of the 80 assessed full-text articles, 70 were excluded for various reasons. Finally, 10 studies met all eligibility criteria and were included in the qualitative synthesis. The selection process followed PRISMA 2020 guidelines, with all exclusions documented (see Figure 1). Several studies investigating relevant interventions were excluded primarily because they reported outcomes for mixed cohorts of CM and SM patients without providing outcome data that could be extracted specifically for the CM subgroup. Of the 10 included studies, six studies featured exclusively CM populations, while four studies reported stratified outcomes for CM subsets within the mixed cohorts.

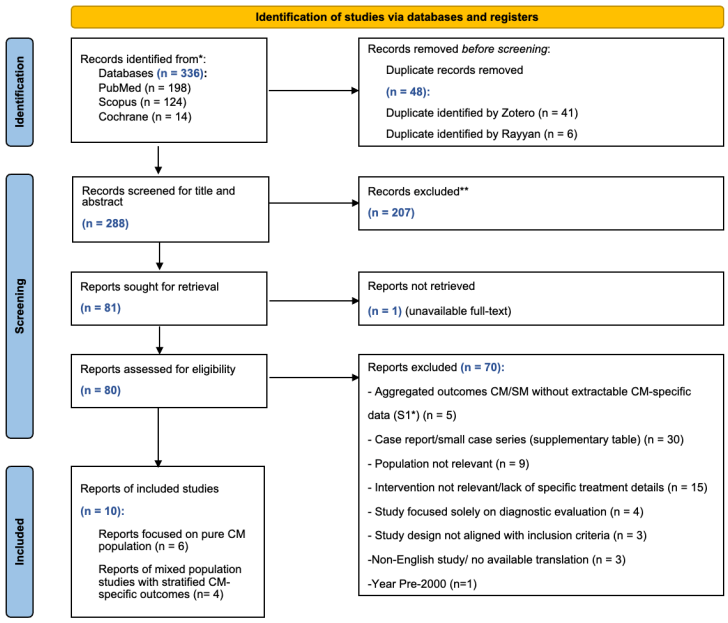

Figure 1 PRISMA flow diagram demonstrates literature selection process

Basic Characteristics of the Included Studies

We included 10 studies which span a publication period from 2003 to 2023 (N=333 CM patients). Of the 10 studies, 6 studies focused on pure CM populations without systemic involvement, while four studies (2 mixed CM/SM, 2 mixed disease) provided stratified CM subgroup outcome data (In such cases we analyzed only the CM relevant subset in accordance with our pre-specified protocol.). There were no randomized controlled trials. Two studies had comparative design (non-randomized), five were cohort studies and three were case series. Most studies (8/10) had sample sizes of 22 or fewer, indicating that the evidence base for interventions in CM was largely built upon small-scale investigations. Gender distribution, available for 305 patients (91.6%), was nearly equal overall (49.5% male, 50.5% female) but it showed a considerable variability between studies. The population was predominantly pediatric, reflecting the epidemiology of CM, while adult data being more limited often focused on persistent MPCM reported as UP and, and in some cases, inferred from mixed cohort studies. The interventions evaluated fell into four broad categories: phototherapies (UVA1,

NB-UVB) (4 studies), topical therapies (corticosteroids, pimecrolimus) (3 studies), systemic therapies (omalizumab and cladribine) (2 studies), and symptomatic therapy (antihistamines/steroids) (1 study). Outcomes assessed include lesion improvement (count, clearance, severity indices), symptom relief (particularly pruritus), quality of life, and adverse events. Follow up duration varied from several months to over 5 years. The key characteristics and findings of the 10 included studies including each study design, population, intervention, key outcomes, summary of effect direction, and risk of bias assessment are synthesized and presented in Table 1.

4.2 Risk of Bias Assessment

Two reviewers (TH, NB) independently assessed all studies. The detailed domain-level judgments are presented in traffic light plots (Figure 2 and 3). Overall, the evidence for interventions in CM is characterized by a majority of studies exhibiting moderate to serious risk of bias, which significantly limits the certainty of conclusions. The most prevalent and serious concern was confounding by the natural history of the disease. As CM can resolve spontaneously, particularly in children, the lack of control groups in most studies likely leads to an overestimation of treatment effects. Common additional limitations included measurement bias, as several studies relied on non-validated or investigator-created outcome scales, and selection bias, due to recruitment from specialty centers, limiting generalizability.

Among ROBINS-I assessed studies, only two studies were judged to have moderate risk of bias. The retrospective comparative study by Patrizi et al. (2015) on topical corticosteroids provided more robust evidence due to its use of a control group, and the prospective pilot on UVA1 phototherapy by Gobello et al. (2003) had a lower risk of bias due to its prospective design and clear protocol." All other ROBINS-I assessed studies (Barete et al., 2015; Calzavara-Pinton et al., 2023; Heide et al., 2007; Lemal et al., 2019; Mashiah et al., 2018) were deemed to have a serious risk of bias, primarily due to the lack of control group, small CM subgroups and measurement limitations (Figure 2). The three-case series were judged to be at a moderate to high risk using the JBI checklist due to significant methodological limitations, including small sample sizes, unclear patient inclusion, and non-validated assessments (Heide et al., 2007; Prignano et al., 2010; Sharquie & Alhyali, 2022) (Figure 3).

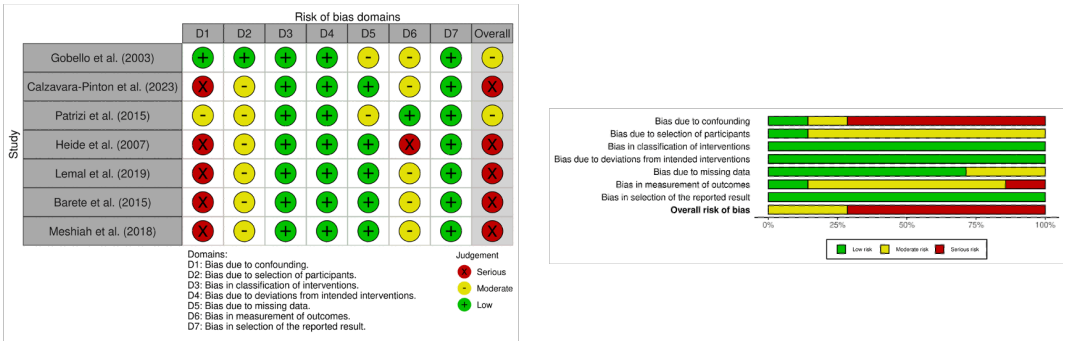

Figure 2 Risk of bias assessment for non-randomized studies of intervention: domain-level judgement and overall summary (ROBINS-I)

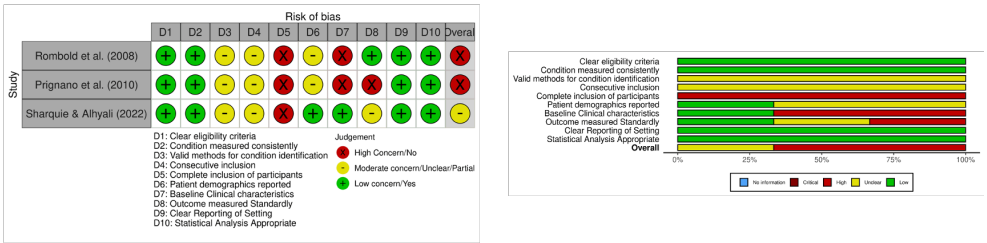

Figure 3 Methodological quality assessment of case series: domain-level judgement and summary of criterion fulfillment (JBI Checklist)

Table 1 Summary of included study characteristics, categorized by intervention type, along with their key design features and findings (studies listed by publication year)

Study	Design	Population	Intervention	Outcomes Measured	Key Findings	Effect Direction Summary	Risk of Bias
I.	**Topical Therapy**						
Heide et al. (2007)	Uncontrolled pilot (using a retrospective cohort design)	11 patients (5 adults, 6 children) with 9 MPCM reported as UP, 1 MPCM TMEP variant, 1 DCM	Fluticasone propionate 0.05% cream (25% diluted) under wet-wrap occlusion for 6 weeks. Adults: (average 8 g.) per day, Children: (average 4 g.) per day	SCORMA skin severity index, Cosmetic improvement (clinical exam), Mast cell counts (assessed at baseline, post treatment 6 weeks and up to 24 weeks	Partial improvement in 9/11 (82%); mean SCORMA decreased from 38 to 26; mast cell counts reduced 10-60%; maintained up to 24 weeks post-treatment. No significant side-effects reported	Positive effect on symptoms and appearance, safe in short term	High
Patrizi et al. (2015)	Retrospective Comparative Cohort	176 children (<15 y) with solitary mastocytoma	Topical clobetasol propionate 0.05% cream (2 weeks) vs. observation ("wait and see")	Lesion resolution, time to heal (follow-up: mean 56.3 months)	No difference in eventual resolution; healing time ~2x faster with steroid (16.4 vs 34.7 months, p=0.001). No side effects reported	Positive: Accelerates healing and controls symptoms.	Moderate
Mashiah et al. (2018)	Retrospective cohort study	18 children (3-42 months) with mastocytomas and MPCM	Topical pimecrolimus 1% cream BID (mean 8.3 months per patients); follow-up 12 months)	Clinical response per lesion (size, elevation, color change), Darier's sign, safety monitoring (assessed every 2 months during treatment, 12 months post-treatment)	Significant improvement in skin lesions. Of 146 lesions treated: 26.7% fully disappeared, 67% lightened in color. Among the 116 papular lesions, 47% became macular. Darier's sign became negative in 14 of 17 patients (82%). No adverse effects were observed.	Positive: Reduces reactivity and improves appearance.	High
II.	**Phototherapy**						
Gobello et al. (2003)	Prospective pilot (non-RCT)	22 adults with MPCM reported as UP	UVA1: high-dose (130 J/cm²×10d) vs medium-dose (60 J/cm²×15d)	Lesion count, mast cell counts, pruritus (VAS), DLQI (assessed at end of treatment, 2 months, 6 months)	Both UVA1 regimens significantly improved pruritus and QoL. No significant difference between high- vs. medium-dose efficacy. Most patients remained in remission at 6 months. No serious side effect, except for mild erythema, and temporary pruritus	Positive effect for symptoms and QoL, neutral for cosmetic appearance.	Moderate
Rombold et al. (2008)	Retrospective Case series	CM subgroup: 19 adults with MPCM among 230 patients with various skin diseases	UVA1 phototherapy (mean 13.8 sessions, total dose 942.63 J/cm²) (mean single dose 72.11 ± 21.49 J/cm²)	Physician-assessed grading scale (-2 to +4) (assessment time points not specified)	57.9% (11/19) showed improvement; well tolerated (mild dryness, hyperpigmentation).	Positive improvement in skin lesions and symptoms.	High
Prignano et al. (2010)	Retrospective Case Series	7 MPCM reported as UP patients (4 pediatric, 3 adult)	NB UVB: 12 sessions/cycle (3 cycles total). Dose adjusted to Fitzpatrick skin type (III/IV): 70–	Clinical assessment of lesions, patient-reported pruritus (assessed after each cycle 12, 24, and 36 sessions)	Marked lesion improvement after 1st cycle; pruritus greatly reduced; NB-UVB well tolerated. No adverse events.	Positive effect reported on both lesions and pruritus improvement.	High

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Study	Design	Population	Intervention	Outcomes Measured	Key Findings	Effect Direction Summary	Risk of Bias
Calzavara-Pinton et al. (2023)	Single-center retrospective observational cohort	CM subgroup: 18 (MPCM reported as UP), among 740 patients with various dermatosis (mean age 17, age range 8-27)	80% of MED initially, escalated by 20% per session Medium dose UVA1. Treatment cycles: 1.2 ± 0.4. Irradiations per cycle: 23.5 ± 8.5. Total cumulative dose: 1816.2 ± 893.3 J/cm².	Physician-assessed: complete remission (CR) or marked improvement (MI) vs no/poor response (assessment time points not specified)	50% (9/18) achieved CR/MI for pruritus; no significant improvement in pigmentary lesions was observed for MPCM subset; Short-term side effects infrequent and mild (transient erythema, pruritus).	Positive effect for symptomatic control, neutral for pigmentation.	High
III.	**Systemic Therapies (Biologic and Cytoreductive agent)**						
Barete et al. (2015)	Retrospective observational cohort study	6 adult CM subgroups (MPCM reported as UP) among a larger mastocytosis cohort (N=68)	Cladribine (0.14 mg/kg/day IV/SC, 1-5 day, repeated every 4-12 weeks)	Clinical response per consensus criteria (CR, MR, PR, NR) (response assessed after each course and 2 months after last course)	Outcome reported as composite ORR in CM subset: 100% (6/6 patients). MR: 4 patients (67%). PR: 2 patients (33%). CR: 0 patients. symptoms. Safety: No treatment-related deaths. Toxicity profile (myelosuppression, infection risk) is a key consideration.	Positive signal on symptoms and lesions in a composite ORR but burdened by high risk of bias and significant toxicity.	High
Lemal et al. (2019)	Prospective cohort study (multi-center)	11 adult CM subgroup patients (extracted from a total cohort of 55 patients with various mast cell disorders	Omalizumab 150-300 mg subcutaneously (SC) every 2 weeks (median 11 months)	Investigator global response (CR/MR/PR); symptom-specific responses (assessed at 2, 6 months)	Best ORR in CM subset: 90.9% (10/11). (MR): 5 patients (45.45%), (PR): 5 patients (45.45%), no Response: 1 patient (9.1%). Final Persistent ORR in CM: 63.6% (7/11 patients).	Positive effect on symptoms but be caution due to potential side effects.	High
IV.	**Symptomatic Therapy**						
Sharquie & Alhyali (2022)	Retrospective descriptive case series	45 pediatric CM patients	Antihistamines + corticosteroids	Symptom relief, physician observation of rash and pruritus, Darier's sign (follow-up period: 2 years)	Pruritus: 100% patients experienced relief with treatment. Severity reduced from moderate/severe to mild/none. Rash improved significantly with treatment. Darier's sign became negative after therapy, indicating decreased mast cell reactivity. No adverse effects.	Positive effect on pruritus and lesions improvement, consistent with the self-limiting nature of pediatric CM, but efficacy vs. natural history cannot be established.	Moderate

[1]CM: Cutaneous Mastocytosis, [2]SCORMA: a semiquantitative scoring system for lesion extent, intensity, and Darier's sign, [3]MPCM: Maculopapular Cutaneous Mastocytosis (also referred to as Urticaria Pigmentosa (UP) in several studies), [4]DCM: Diffuse Cutaneous Mastocytosis, [5]TEMP: Telangiectasia Macularis Eruptiva Perstans, [6]CM subset outcome extractable: Data specific for CM/MPCM patient subgroup were able to be extracted from a larger study population, [7]VAS: Visual Analog Scale for pruritus, [8]DLQI: Dermatology Life Quality Index, [9]CR/MR/PR/NR: Complete Response/Major Response/Partial Response/No Response, as defined by consensus criteria, [10]ORR: Overall Response Rate (a composite of CR+MR+PR)

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4.3 Synthesis of Findings by Intervention Type

4.3.1 Symptomatic Therapies (Antihistamines and Corticosteroids)

In a large descriptive case series of 45 children with pure CM managed conservatively with H1-antihistamines for itch and short courses of topical and/or oral corticosteroid for severe flares, all patients experienced relief of pruritus and lesion stability over a 2-year follow-up, with most achieving eventual disease remission (Sharquie & Alhyali, 2022).

4.3.2 Topical Therapies (Corticosteroids and Calcineurin Inhibitors)

Evidence for topical corticosteroids came from two studies that demonstrated partial efficacy. Heide et al. (2007) performed a small pilot study using fluticasone 0.05% cream diluted to 25% potency, applied under wet-wrap occlusion for 6 weeks in 11 patients (5 adults, 6 children). Most patients (9 of 11) showed visible lesion improvement (light color, flatter lesions) and symptom reduction after treatment. The number of mast cells decrease between 10-60%. The average severity score (SCORMA index) dropped from 38 at baseline to 26 after treatment, indicating a moderate reduction in disease severity. However, the benefits were partial, and improvement often fell short of patient expectations. The use of diluted fluticasone under wet wrap (a technique to enhance penetration) was well tolerated and can be a potential option for patients (particularly children) with widespread MPCM. A complementary perspective comes from moderate risk of bias study by Patrizi et al. (2015), which retrospectively compared 91 children treated with topical corticosteroids (mostly clobetasol 0.05% intermittently) to 85 children managed by observation only among 176 pediatric patients with solitary mastocytoma, over an average of 56.3 months follow-up. The time to complete resolution was significantly shorter with steroid therapy: about 16 months on average versus 34.7 months with observation (p value = 0.001). Although treatment did not change the healing outcomes of the lesions, the time to improvement was significantly shorter with steroid application. No adverse effects of topical clobetasol were observed. Patrizi et al. (2015) highlighted that an intermittent short course (clobetasol for 2 weeks in those > 1 year old) can be considered safe and effective.

Topical calcineurin inhibitors, particularly pimecrolimus 1% cream, have emerged as a useful steroid-sparing option for CM in children. Mashiah et al. (2018) conducted an uncontrolled retrospective cohort study with 18 infants and young children with CM (mean age 16.9 months; mixture of solitary mastocytoma and MPCM lesions), with a total of 146 lesions. Treatment was applied twice daily on the lesions, and follow-ups were conducted every 2 months, with an assessment 12 months after treatment cessation (treatment duration ranged from 3-16 months, with a mean of 8.3 months per patient). Of the 146 lesions, 39 lesions (26.7%) completely disappeared, 98 lesions (67%) significantly faded or only left hyperpigmentation. Darier's sign became negative in 14 out of 17 patients tested (82%). No significant side effects or local irritation were reported.

4.3.3 Phototherapy

Three studies supported the use of UVA1 in CM; together, they provided a robust, multi-decade perspective on its clinical utility. Gobello et al. (2003) conducted a non-randomized pilot trial in 22 adults with MPCM, reported as UP patients comparing high-dose UVA1 (130J/cm^2 per session, 10 sessions over 2 weeks) with medium-dose UVA1 (60 J/cm^2 per session, 15 sessions over 3 weeks). Follow-up assessments were conducted at the end of treatment, and at 2 and 6 months post-treatment. They found no significance difference in outcomes between the two dose regimens. Clinically, pruritus improved considerably (20/22 patients, P<0.004) and quality of life scores (Skindex-29) improved significantly by the end of treatment (P<0.03). However, the number of visible lesions did not significantly decrease in most patients (P>0.05). Tolerability was good, no severe side effects were reported, aside from mild transient erythema in some cases. Two other retrospective studies corroborate these findings. Rombold et al. (2008) analyzed UVA1 phototherapy in a subgroup of 19 adult CM patients (mean age: 41.37 ± 12.1 years), with a confirmed diagnosis of MPCM reported as UP. This subgroup received a mean of 13.8 ± 3.68 irradiation sessions with a medium-dose UVA1 regimen. Improvement in their skin disease and symptoms was observed in 57.9% (11/19) of patients. Among responders, 21.1% (4/19) had substantial improvement, 26.3% (5/19) had

moderate improvement, and 10.5% (2/19) had slight improvement, although no patients achieved complete healing of lesions. A more recent UVA1 study is by Calzavara-Pinton et al. (2023). This retrospective cohort study reported outcomes for the 18 CM-subset patients with MPCM reported as UP (8 males, 10 females, age range 8-27 years) treated with medium dose UVA1. The treatment led to marked improvement or complete remission in 50% of patients, mirroring the findings of Rombold et al. (2008). They noted that the treatment mainly improved functional symptoms such as pruritus and flares but had little effect on the persistent pigmentation of lesions. Acute adverse effects were minor and manageable, with two patients discontinuing due to disease worsening (non-treatment-related).

As for NB-UVB phototherapy, the evidence is limited to a small case series with a serious risk of bias due to methodological limitations (Prignano et al., 2010). Within this uncontrolled study, they treated seven patients (4 children, 3 adults) with MPCM using NB-UVB administered three times weekly for 12 weeks. After 36 sessions, all patients demonstrated dramatic clinical improvement including visible lightening of lesions and marked pruritus reduction, with no mention of adverse effects. Notably, prior to NB-UVB treatment, these patients' symptoms were not controlled with antihistamines alone. The finding suggests that NB-UVB may be an effective and safe symptomatic therapy; however, the very small sample size and lack of a control group limit the strength of this evidence.

4.3.4 Systemic therapies (Biologics and Cytoreductive agent)

Systemic treatments were considered in CM primarily when the disease was extensive, refractory, and symptoms were severe and could not be controlled by topical or physical modalities. We identified evidence for two distinct systemic approaches: an IgE-targeted biologic (omalizumab) by Lemal et al. (2019), and a cytoreductive chemotherapeutic agent that reduces mast cells (cladribine) reported by Barete et al. (2015).

Omalizumab (anti-IgE): Lemal et al. (2019) conducted a prospective multicenter cohort study of 55 patients with various mast cell disorders, including mastocytosis and mast cell activation syndromes. Outcomes were stratified and reported separately for the 11 patients with CM. Omalizumab (150-300 mg every 2 weeks) elicited an overall response in 10/11 CM patients (90.9%): five (45%) had a major response and five (45%) had partial response. Responses were durable as 7/11 patients (63.6%) had a persistent response at the last follow-up. Omalizumab appeared particularly effective for relieving cutaneous and superficial vasomotor symptoms (pruritus, flushing). Adverse effects were reported for the whole cohort, and were mostly mild, aside from one patient who developed a severe reaction (laryngeal edema after the first injection). While these findings suggest that omalizumab may be beneficial for symptomatic control in CM, this evidence comes from a study with serious risk of bias due to small CM subgroup, which may confound the high response rates reported.

Cladribine (2-CdA): Barete et al. (2015) conducted a multicenter retrospective cohort study of 68 patients with various mastocytosis subtypes and reported outcomes separately for a small CM subgroup (n=6). They administered cladribine in 1-9 courses, median 3.7 courses. The dosage given was 0.14 mg/kg/day, administered as a 2-hour infusion or subcutaneously for 1 to 5 days, which defined a course of treatment. Anti-infective prophylaxis was given during and after treatment due to its immunosuppressive effects. Outcomes were measured as treatment response according to established consensus criteria (a composite score). All 6 patients responded (ORR 100%, 2 (33%) achieving a major response and 4 (67%) a partial response). Symptomatically, there were significant improvements in flushing, pruritus and urticaria. No treatment-related deaths occurred, but notable myelosuppression and infection risks were observed.

4.4 Harvest Plot of Treatment Effects

Figure 4 presents a harvest plot summarizing the direction and consistency of treatment effects across all included studies. This visual summary categorized studies by intervention type, with each bar representing a study, the bar height corresponding to the sample size (N). The fill pattern indicates the reported outcome for symptom relief (top panel) and lesion improvement (bottom panel): solid fill indicates

a positive effect, hatched fill indicates no significant effect, and an open bar would denote a negative effect (none were reported).

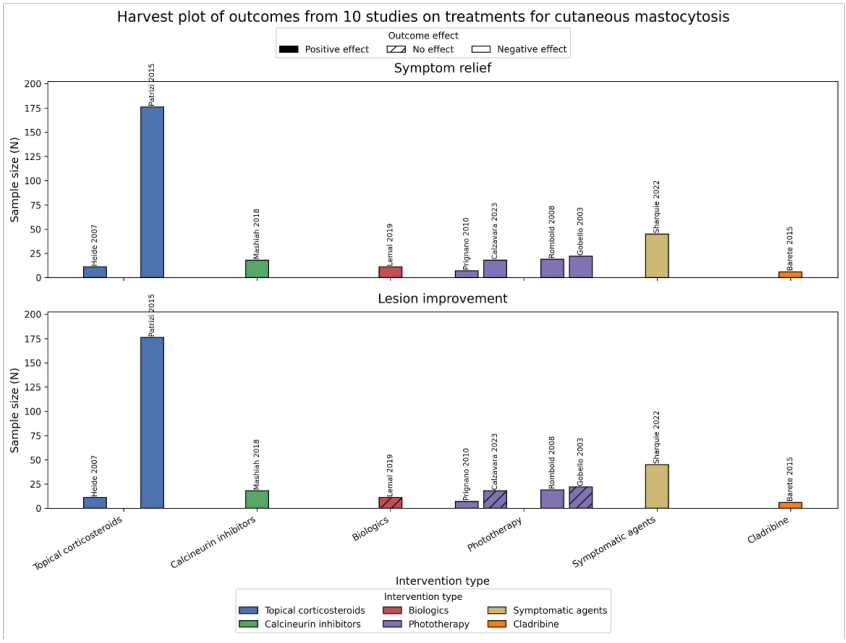

Figure 4 Harvest plot of Symptom and lesion Improvement Categorized by Intervention Types

5. Discussion

5.1 Summary of Findings and Evidence Challenges

In this narrative systematic review, we synthesized evidence from 10 studies on various treatments for CM. The interventions evaluated ranged from skin-directed therapies (topical therapies, phototherapy) to systemic drugs (omalizumab, cladribine). Because no RCTs were eligible, our review is essentially a narrative synthesis of observational evidence. CM management strategies must account for the variable disease course and the predominantly low-level evidence base. Despite the diverse designs and patient populations, a coherent picture emerged, showing that multiple therapeutic strategies can achieve meaningful improvement in CM, particularly in relieving symptoms. We structured our discussion by intervention type to highlight clinical decision-making considerations. However, a recurring challenge in synthesizing the evidence for CM must be acknowledged: many clinical trials enrolled mixed populations of patients (CM/SM) without stratifying outcome data for the CM subgroup. Several high-quality studies of potent agents, including cladribine (Bugaut et al., 2024), masitinib (Paul et al., 2010), rupatadine (Siebenhaar et al., 2013), the topical raft modulator miltefosine (Hartmann et al., 2010), and PUVA versus NB-UVB (Brazzelli et al., 2016) were excluded from our primary analysis. The promising aggregate results from these trials highlight both a potential therapeutic avenue and a critical methodological shortcoming in the existing literature.

5.2 Interpretation of Findings by Intervention Type

5.2.1 Symptomatic Therapies:

First-line management of CM typically involves symptomatic control to alleviate pruritus and stabilizing mast cells to prevent degranulation. The evidence for this approach is derived from a large descriptive case series in pediatric CM (Sharquie & Alhyali, 2022), which reported universal symptom improvement with antihistamines and corticosteroids as needed. This aligns with the expected benign natural

history of pediatric CM. However, as an uncontrolled descriptive study assessed using the JBI checklist, it carries a moderate risk of bias.

5.2.2 Topical Therapies:

Topical anti-inflammatory agents, including corticosteroids and calcineurin inhibitors, are among the first-line options for localized or pediatric CM due to their direct action on skin mast cells and favorable safety profile (Czarny et al., 2018). The comparative study by Patrizi et al. (2015) provides the most robust evidence, showing significant acceleration of healing with clobetasol versus observation, though the study remains at moderate risk of bias. Meanwhile, pimecrolimus offers an effective steroid-sparing alternative with favorable safety in children (Mashiah et al., 2018). Collectively, these studies illustrate that topical therapies may improve CM lesions, with favorable safety. Pimecrolimus appeared particularly effective for pediatric CM, while intermittent topical clobetasol application shortened disease duration in mastocytoma. However, neither agent can entirely cure extensive MPCM (lesions often persist, albeit paler and less reactive). Thus, topical therapy is best suited as a safer long-term management approach for localized disease management.

5.2.3 Phototherapy:

UVA1 consistently improves pruritus and quality of life in adult MPCM patients across 3 studies, although pigmentation changes are minimal (Calzavara-Pinton et al., 2023; Gobello et al., 2003; Rombold et al., 2008). The evidence base, while consistent in direction, derives from studies with moderate to serious risk of bias. Although positive effects were reported, confounding by natural history and the use of subjective outcomes are significant limitations. On the other hand, NB-UVB shows promise for lesion clearance but is supported by only one small case series (Prignano et al., 2010), representing very limited evidence that requires confirmation from future studies. In summary, phototherapy (UVA1, NB-UVB) is a viable second-line option for symptomatic control in CM. UVA1 has more robust evidence supporting its role in alleviating pruritus and improving quality of life, while NB-UVB may offer additional benefits for lesion clearance, though the evidence is preliminary.

5.2.4 Systemic Therapies:

Both omalizumab and cladribine demonstrate high response rates in severe refractory CM. Omalizumab (90.9% response in 11 CM patients) offers a targeted and generally well-tolerated option for controlling debilitating mediator symptoms (Lemal et al., 2019). In contrast, cladribine (100% response in 6 CM patients) can induce substantial disease remission but carries significant toxicity, limiting its use to the most exceptional circumstances (Barete et al., 2015). However, the certainty of evidence for both agents is low, constrained by a serious risk of bias and derived from a very small CM subgroup with highly selected refractory disease (confounding by indication).

5.3 Synthesized Patterns and Visual Summary

We interpret these findings with caution, acknowledging the serious methodological limitations of the included studies and the potential for confounding by natural history, particularly in pediatric populations. Nevertheless, a consistent, positive effect direction was observed across all intervention categories, with all studies reporting improvements in symptoms (notably pruritus) or lesions, and essentially no studies reporting worsening outcomes. This consistency in reported improvement, visualized in harvest plot (Figure 4), is encouraging, but the true magnitude of the therapeutic benefit remains uncertain. This is particularly relevant for pediatric studies, where spontaneous regression is common and may confound observed treatment effects. Key clinical patterns emerged from the synthesis. Analyses revealed that management should be tailored significantly by age and disease phenotype.

Symptom control versus lesion clearance: Most therapies, including phototherapy and omalizumab, effectively alleviate mediator-related symptoms (pruritus, flushing) but have limited impact on lesion

resolution (although lesions may become lighter or less raised). In contrast, interventions like cladribine or potent topical corticosteroid can reduce lesion burden, though cladribine carries greater risks.

Age-based management: Evidence supports a divergent approach by age. Pediatric CM, often self-limited, is effectively managed with conservative first-line therapies (topical therapies, symptomatic therapies). Adult CM, typically persistent, more frequently requires second-line options like phototherapy or systemic agents (omalizumab, cladribine) for adequate control.

5.4 Comparison with other Treatment Modalities

Several other therapeutic options for CM have been reported in the literature but were not captured in our included studies. Laser therapy: Pulsed dye laser and other laser modalities have been described anecdotally for cosmetic improvement of persistent pigmentation but did not meet our inclusion criteria (Bedlow et al., 2000; Siddique et al., 2017). They may be considered for select cases where lesion appearance is a primary concern. Oral antihistamines and cromolyn sodium are commonly used empirically for systemic mast cell disorders. However, evidence for these approaches in isolated CM is limited and confined to case reports (Horan et al., 1990). PUVA phototherapy, whose efficacy was reported in older literature, was not represented in our included studies (Godt et al., 1997). Its use has declined with more targeted modalities like UVA1 and NB-UVB. Likewise, emerging therapies such as tyrosine kinase inhibitors (e.g., imatinib, avapritinib) show promise in advanced SM but remain unexplored in isolated CM and should be considered investigational (Hoffmann et al., 2008; Lee et al., 2021). These gaps highlight important areas for future research and underscore that our review's scope, while comprehensive for published studies meeting the inclusion criteria, does not encompass all treatments used in clinical practice. In addition, case reports and small case series describing other therapeutic approaches, including laser therapies, PUVA, and emerging targeted agents, are summarized in supplementary Table S1.

5.5 Overall Certainty of Evidence and Limitations

Across all interventions, the certainty of evidence was low. The judgment is based on the consistently serious risk of bias in the included studies (primarily due to uncontrolled designs and confounding by the disease's natural history), imprecision from very small sample sizes, inconsistency from variety of outcomes measured, and the indirectness of evidence from mixed population studies where CM-specific data were extracted from subgroups. Additionally, the lack of standardized outcome measures from treatment response in CM is a major limitation. Studies used variable endpoints (pruritus VAS, DLQI, SCORMA, investigator-assessed response, lesion counts, and time to resolution), making cross-study comparisons difficult and precluding meta-analysis.

Although findings across studies were somewhat consistent in showing positive direction of effect, the methodological limitations mean the true magnitude of efficacy is uncertain. Therefore, the findings of this review should be interpreted cautiously and are best viewed as generating hypotheses for future rigorously controlled trials.

6. Conclusions

This narrative systematic review synthesized the available evidence from ten studies on treatments for CM. A consistent positive effect direction was observed across all intervention categories, including topical therapies, phototherapy and systemic agents for improving symptom relief and, to a variable degree, cutaneous lesions. The certainty of this evidence is low, constrained by the absence of randomized controlled trials, small sample sizes, and study designs unable to control for the strong confounding effect of the disease's natural history. Consequently, there is a need for high quality, controlled trials in well-defined CM populations using validated cutaneous-specific outcome measures.

For clinical practice, a stepwise individualized approach is supported by the synthesized evidence:

- First-line management should consist of symptomatic control with H1/H2 antihistamines and topical corticosteroids or pimecrolimus, particularly in pediatric patients.

- Second-line therapy for extensive skin involvement may include phototherapy (UVA1, NB-UVB), which offers symptomatic relief with a favorable safety profile.
- Systemic therapies with omalizumab should be reserved for severe, refractory cases with a significant impact on quality of life, while cytoreductive agents like cladribine are limited to the most exceptional circumstances due to their significant toxicity profile.

Ultimately, treatment selection must be tailored to disease severity, patient age, symptom profile, and therapeutic goals, with the understanding that the evidence base for these decisions requires strengthening with more rigorously controlled trials.

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8. Appendices

8.1 Appendix 1. Full Search Strategies for Each Database

Database	Search Strategy	Journal
PubMed	((((("Mastocytosis, Cutaneous"[Mesh]) OR "cutane* mastocytos*" OR "mastocytos*, cutane*" OR "skin mastocytos*" OR "urticaria pigment*" OR "mastocytom*" OR "diffuse cutaneous mastocytos*")) AND ((("Therapeutics"[Mesh]) OR "treat*" OR "therap*" OR "drug therap*" OR "medicat*" OR "therapeut*" OR "manag*" OR "antihistamine*" OR "corticosteroid*" OR "biologic*" OR "omalizumab" OR "immunotherap*" OR "laser therap*" OR "mast cell stabiliz*" OR "PUVA" OR "light therap*" OR "topical therap*" OR "systemic therap*"))) AND ((("Treatment Outcome"[Mesh] OR "symptom* relief" OR "clinic* outcome" OR "disease progress*" OR "treatment respons*" OR "advers* event*" OR "long-term outcome*" OR "quality of life" OR "remiss*")))	198
Cochrane	Search keywords: ("cutaneous mastocytosis" OR "skin mastocytosis" OR "mastocytosis, cutaneous" OR "mastocytoma" OR "diffuse cutaneous mastocytosis" OR "urticaria pigmentosa") AND ("treatment" OR "therapy" OR "intervention" OR "drug therapy" OR "medication" OR "therapeutics" OR "management" OR "biologics" OR "immunotherapy" OR "laser therapy" OR "topical treatment" OR "systemic treatment") AND ("symptom relief" OR "clinical outcomes" OR "disease progression" OR "quality of life" OR remission OR "treatment response" OR "adverse event")	14
Scopus	(TITLE-ABS-KEY ("cutaneous mastocytosis" OR "skin mastocytosis" OR "urticaria pigment*" OR "mastocytosis, cutaneous" OR "mastocytoma" OR "diffuse cutaneous mastocytosis")) AND (TITLE-ABS-KEY (antihistamines OR corticosteroids OR biologics OR "laser therapy" OR "PUVA" OR "light therapy" OR "mast cell stabilizers")) AND (TITLE-ABS-KEY ("symptom relief" OR "clinical outcomes" OR "disease progression" OR "quality of life" OR remission OR "treatment response" OR "adverse events"))	124