CUTANEOUS MASTOCYTOSIS THERAPEUTIC CHALLENGES AND OPPORTUNITIES IN ADVANCED TARGET NANOCARRIER SYSTEM

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Abstract

Cutaneous mastocytosis (CM) is a rare skin disorder characterized by abnormal mast cell accumulation, leading to symptoms such as pruritus, flushing, erythema, urticaria, and occasionally blistering. It is primarily associated with activating mutations in the KIT proto-oncogene, particularly D816V, resulting in uncontrolled mast cell proliferation. CM is classified into maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis, and solitary mastocytoma, and although generally benign, it significantly impacts patient quality of life. Diagnosis involves clinical evaluation, Darier's sign, skin biopsy, and laboratory investigations including serum tryptase and KIT mutation analysis. Current treatments are mainly symptomatic, including antihistamines, topical corticosteroids, calcineurin inhibitors, mast cell stabilizers, and phototherapy, with biologics and tyrosine kinase inhibitors used in refractory cases. However, these therapies are limited by poor skin penetration and lack of targeted delivery. The stratum corneum acts as a major barrier to drug delivery, restricting drug access to dermal mast cells. Nanotechnology-based systems such as liposomes, niosomes Transethosomes, solid lipid nanoparticles, and nanostructured lipid carriers offer enhanced permeation, controlled release, and targeted delivery. These advanced approaches represent a promising strategy for improving therapeutic outcomes in cutaneous mastocytosis.

Keywords

Cutaneous mastocytosis; Mast cells; KIT mutation; Darier's sign; Topical drug delivery; Nanotechnology; Niosomes; Liposoms Transethosomes; Solid lipid nanoparticles; Nanostructured lipid carriers; Skin barrier; Dermal drug targeting; Histamine; Phototherapy

Introduction

Cutaneous mastocytosis (CM) is a rare skin disease that involves the infiltration and proliferation of mast cells in the skin. Mast cells are immune cells originating from hematopoietic progenitor cells and are involved in allergic and inflammatory reactions via the release of mediators like histamine, cytokines, proteases and leukotrienes1. In CM, the infiltration of mast cells results in a wide range of cutaneous symptoms, such as pruritus, erythema, flushing, urticaria and, in extreme cases, blistering as a consequence of massive mediator release1, 2 .The development of cutaneous mastocytosis is closely linked to activating mutations in the KIT proto-oncogene, especially the D816V mutation, resulting in mast cell hyperproliferation and survival1, 3. CM can be broadly divided into maculopapular cutaneous mastocytosis (also called urticaria pigmentosa), diffuse cutaneous mastocytosis and solitary mastocytoma, based on clinical presentation.2 Maculopapular cutaneous mastocytosis is the most frequent type of CM seen in both adults and children2. While CM is generally regarded as a benign disorder, it has a profound impact on patient quality of life, since it is accompanied by pruritus, cosmetic concerns and the potential for systemic symptoms following mast cell degranulation and mediator release3 .Current approaches focus primarily on symptomatic treatment and limiting mast cell degranulation and mediator release rather than addressing the pathology of the disease. Topical H1 and H2 antihistamines, topical corticosteroids and mast cell stabilizers (e.g., cromolyn sodium) are used as first-line treatments1,4.Second-line therapies include phototherapy (e.g., PUVA, narrowband UVB radiation), calcineurin inhibitors and biologic therapies (e.g., omalizumab)4.Although these treatments are available, traditional therapies have a number of drawbacks, including limited penetration into the skin, short half-life, systemic side effects and an inability to specifically target mast cells5.The outermost layer of the skin (stratum corneum) provides a significant barrier to drug penetration, thereby restricting the effectiveness of topical treatments in delivering sufficient drug concentrations to the deeper skin layers, where mast cells are predominantly found6.As a

result, there is an increasing demand for novel drug delivery strategies to improve dermal drug targeting, bioavailability and reduce side effects.

In recent years, nanotechnology-based drug delivery systems have emerged as a promising approach for improving the topical treatment of dermatological disorders, including cutaneous mastocytosis. Nanocarriers such as liposomes, niosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanoparticles offer several advantages, including enhanced skin permeation, controlled and sustained drug release, improved stability, and targeted delivery to specific skin layers[6,7].These systems can effectively bypass the stratum corneum barrier and facilitate the accumulation of therapeutic agents in the dermis, thereby improving treatment outcomes. Among these, niosomes—non-ionic surfactant-based vesicular systems—have gained particular attention due to their superior stability, high drug entrapment efficiency, and ability to enhance skin retention of both hydrophilic and lipophilic drugs[7].Such nano-based systems are especially relevant in the context of topical therapies aimed at modulating mast cell activity and reducing inflammatory responses in CM.

Therefore, the integration of nanotechnology with topical drug delivery represents a novel and promising strategy for the effective management of cutaneous mastocytosis. This review aims to provide a comprehensive overview of current treatment approaches for CM and to highlight recent advances in transethosome -based topical drug delivery systems that offer improved therapeutic efficacy and patient outcomes.

Mastocytosis is a rare disorder characterized by the abnormal accumulation of mast cells in various tissues and is broadly classified into cutaneous mastocytosis (CM) and systemic mastocytosis (SM). Cutaneous mastocytosis includes subtypes such as maculopapular cutaneous mastocytosis (MPCM), also known as urticaria pigmentosa, diffuse cutaneous mastocytosis (DCM), and solitary cutaneous mastocytoma. Isolated cutaneous mastocytosis without systemic involvement is uncommon in adults. Data from a Swedish population-based registry study indicate that urticaria pigmentosa/MPCM is the most frequently reported subtype, accounting for 42% (853 patients) of cases. In adults aged ≥20 years, the annual incidence of mastocytosis is approximately 1.56 per 100,000 population, with a prevalence of 23.9 per 100,000 population. The condition appears to affect females more commonly (59.4%) than males (40.6%), with a mean age at diagnosis of 50.6 years.

Although cutaneous mastocytosis is generally considered benign, patients may experience significant morbidity due to the release of mast cell mediators and the presence of associated systemic conditions. Common clinical manifestations include pruritus, flushing, urticaria, dermatographism, gastrointestinal disturbances, occasional anaphylaxis, and considerable cosmetic and psychological burden. The Swedish study also demonstrated that patients with mastocytosis have a higher burden of comorbidities compared to the general population. Based on the Charlson Comorbidity Index (CCI), 79.6% of patients had no comorbidities, 8.2% had mild comorbidity, and 12.3% had severe comorbidity (CCI ≥2), whereas in the control population, 88.0% had no comorbidity and only 6.6% had severe comorbidity. The most commonly associated conditions included cancer (8.5%), diabetes (3.7%), chronic pulmonary disease (3.4%), and a significantly increased incidence of renal disease.

The prognosis of cutaneous mastocytosis is generally favorable, particularly for benign subtypes. The Swedish registry reported a 5-year survival rate of 96.3% for benign cases, 85.9% for mixed subtypes, and 66.5% for advanced disease. Overall, patients with mastocytosis exhibited slightly lower survival compared to the general population (90.1% vs 94.8% at 5 years), although mastocytosis itself was rarely the direct cause of death. Among 285 recorded deaths, the most common causes were malignant tumors (39%) and cardiovascular diseases (26%), with only 12 deaths directly attributed to mastocytosis.[26]

Pathophysiology of Cutaneous Mastocytosis

Cutaneous mastocytosis is characterised by an increase in mast cells in the skin. Mast cells originate in the bone marrow from multipotential myeloid progenitors. These cells are released into the bloodstream and complete their maturation and gain tissue-specificity. A major mechanism for the development of cutaneous mastocytosis is mutation of the c-kit proto-oncogene, which codes for the KIT receptor (CD117), a transmembrane tyrosine kinase receptor protein that is essential for mast cell survival, differentiation and activation. KIT is activated by the stem cell factor (SCF).

Mastocytosis is caused by activating mutations of c-kit which result in spontaneous activation of the receptor (without its ligand) and abnormal mast cell survival and expansion in the skin.

The most frequent mutation in mastocytosis is KIT D816V, particularly in adults, but it can also be found in children with cutaneous mastocytosis, and other mutations in the extracellular and juxtamembrane regions of c-kit. This points to a clonal disease in both adults and children. Skin mast cells accumulate and on activation (spontaneous or not) release various mediators. These include preformed mediators such as histamine, tryptase, heparin, serotonin, proteases and the products of new synthesis such as prostaglandins, leukotrienes, cytokines and growth factors. These cause vasodilation, vascular leakage, pruritus, erythema, blisters, inflammation and tissue remode, which accounts for the clinical symptoms of cutaneous mastocytosis.

Mast cells may degranulate in response to a broad variety of chemical and physical stimuli, such as mechanical (rubbing, pressure), heat, sudden temperature change, stress, opioids, non-steroidal anti-inflammatory drugs, local anesthetics and insect stings. This explains the worsening of symptoms on rubbing of the lesions (Darier's sign) or of triggers. Skin mastocytosis is usually limited to the skin surface in children and clears at puberty. However, in adults the skin may be part of a systemic disease and the disease is usually persistent.25

Sr. No.	Type	Sub-class
1.	Cutaneous mastocytosis (CM)	1. Maculopapular cutaneous mastocytosis (MPCM) 2. Polymorphic variant 3. Diffuse cutaneous mastocytosis (DCM) 4. Cutaneous Mastocytoma
2.	Systemic mastocytosis (SM) Non-advanced forms of SM	1. Indolent systemic mastocytosis 2. Bone marrow mastocytosis (BMM) 3. Smoldering systemic mastocytosis (SSM)
3.	Advanced forms of SM	1. SM with an associated hematologic neoplasm (SM-AHN) 2. Aggressive SM (SM-AHN)

		3. Mast cell leukemia (MCL)
4.	Mast cell sarcoma (MCS)	

Table 1. Updated Classification of Mastocytosis.

Skin Anatomy and Barrier Function

Stratum corneum is the most prominent barrier to the permeation of drugs through the skin. It is the most peripheral layer of the epidermis and is comprised of terminally differentiated keratinocytes arranged in a compact and dense manner which limits the penetration of endogenous and exogenous substances. The highly specialized structure serves as a protective layer that prevents the penetration of foreign substances and helps to maintain skin homeostasis by regulating the amount of transepidermal water loss and protecting the body against environmental attack. The distinctive structural arrangement of the stratum corneum makes medications penetrate the skin via three main pathways: intercellular, transcellular, and appendageal pathways, which are depicted in Fig. 1. Among these, intercellular route is the pathway which is said to be the most dominant route of transdermal drug delivery. In this route, molecules of drugs diffuse through the lipid-rich matrix that exists between the closely stacked keratinocytes of the stratum corneum. This pathway is especially favorable to small, lipophilic drug molecules because they have a high affinity to the lipid domains.[8,9]

The transcellular route on the other hand comprises the direct transit of drug molecules through the keratinocytes. In this pathway, drugs must cross the lipophilic cell membranes, then the hydrophilic intracellular contents, in a sequence of steps, making it a difficult pathway to drug permeation due to repeated partitioning barriers2.The appendageal pathway uses skin appendages like hair follicles and sweating (sudoriferous) glands to transport drugs. Even though these appendages only cover a relatively small proportion of the overall skin surface area, they do provide an alternative pathway to avoid the stratum corneum barrier. This route has obtained a special significance in the delivery of particulate systems, such as nanoparticles and vesicular carriers, which can selectively accumulate in the hair follicles and glandular structures[10],

[11]. Below the epidermis lies the dermis, which is also thicker or thinner depending on the location of the skin and is mainly responsible of the mechanical strength and elasticity of the skin. Dermis consists of a high content of collagen (around 70 percent) and elastin fibers, blood vessels, lymphatic vessels and immune cells. The elimination of metabolic waste and toxins in the lymphatic system is one of its most important physiological functions.[30] The innermost layer of the skin is the hypodermis, mainly composed of adipose tissue, and acts as a thermal insulator, shock absorber, and conduit of nerves and blood vessels.[12]

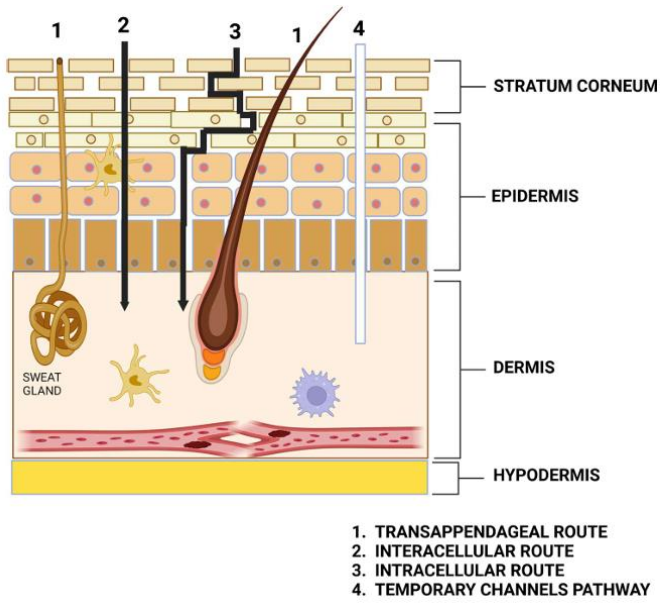

Fig. No. 1: Structure of human skin

Source: Shreenivasan Raagul et al AAPS PharmScitech 26.1 (2025): 41

Mastocytosis is a rare and heterogeneous disorder group in which the abnormal growth, development and activation of mast cells occur in one or more tissues, such as skin, bone marrow, liver, spleen and gastrointestinal tract13. The mast cells are the immune cells that are formed in the bone marrow and play a very important role in the allergic and inflammatory responses since they release various mediators including histamine, tryptase, cytokines, prostaglandins and leukotrienes14.In mastocytosis, excessive deposition and activation of such cells lead to a wide range of clinical manifestations such as pruritus, flushing, urticaria, abdominal pains, anaphylaxis, and, in severe cases, organ dysfunction13,15.

Mutations in the receptor tyrosine kinase, KIT proto-oncogene, required to enable the growth and survival of mast cells has been closely associated with the pathogenesis of mastocytosis. The most typical mutation, KIT D816V, involves constitutive activation of the receptor leading to uncontrolled proliferation and resistance to apoptosis of mastocytes.[16] According to the extent of organ involvement and clinical presentation, all mastocytoses are generally classified as either cutaneous mastocytosis (CM) or systemic mastocytosis (SM) according to the World Health Organization (WHO) classification system.[17]

Based on the level of organ involvement and presentation, the World Health Organization (WHO) has divided mastocytosis according to the WHO into two major groups; cutaneous and systemic mastocytosis. Cutaneous mastocytosis is a disease that is characterized by the presence of mast cells which are limited to the skin without any indication of systemic involvement and often followed by a benign and self-limiting course. Most common subtype of cutaneous mastocytosis is the so-called maculopapular cutaneous mastocytosis, so-called urticaria pigmentosa, which, when present, appears as hyperpigmented macules or papules and usually is accompanied by the Darier sign, which is a wheal-and-flare reaction to mechanical irritation. This subtype may once again be subdivided into monomorphic and polymorphic, where the former is more common in adults and the latter in children.13,17

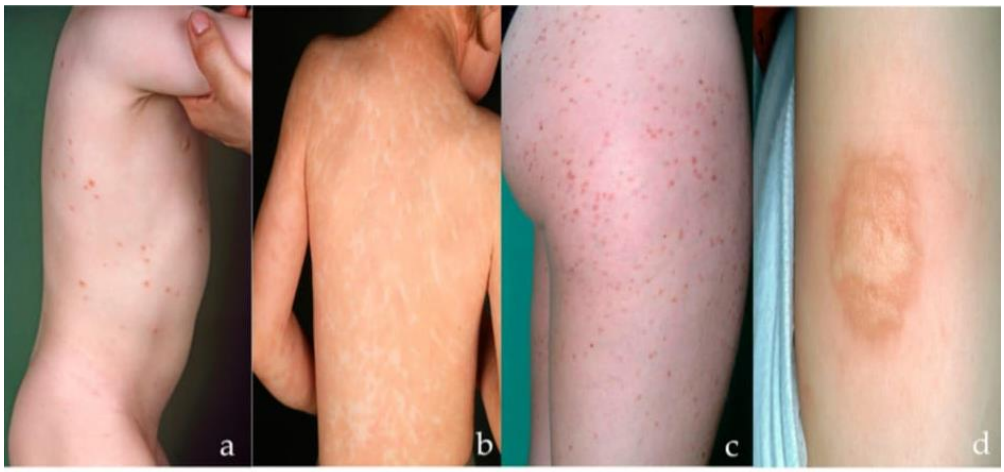

Fig No. 2 (a) Multiple disseminated asymmetric sharply defined flat red-brown macules in a child with childhood maculopapular cutaneous mastocytosis (MPCM). (b) Skin lesions may also be few or numerous with different sizes and shapes. A child with multiple disseminated light-brown plaques is shown as a presentation of MPCM. (c) Disseminated small red-brown macules or slightly elevated papules on the thigh typical

for adult-onset MPCM. (d) Solitary yellowish-red-brown plaques of a mastocytoma in a child, with whealing along the stroke line of a wooden spatula only in involved skin, recognized as a positive Darier's sign.

Source : Brockow, Knut, et al. Diagnostics 14.2 (2024): 161.

Besides maculopapular cutaneous mastocytosis, there are other forms such as diffuse cutaneous mastocytosis; a rare and severe type of mastocytosis that causes extensive mast cell infiltration of the skin resulting into thickening, erythema, and the formation of blisters, especially in infants. One more subtype is solitary mastocytoma that is presented by the localizedsaccus mast cell-accumulation forming a single lesion and usually resolves on its own without the need of aggressive treatment. Though cutaneous mastocytosis is typically confined to the skin, it is important to recognize that some cases of cutaneous mastocytosis may be related to or progress to systemic disease and hence should be carefully evaluated in the clinic.[15,13]

Systemic mastocytosis, in contrast, is characterized by the involvement of extracutaneous organs, most commonly the bone marrow, liver, spleen, and gastrointestinal tract and is more commonly diagnosed in adults. It is commonly linked to the activation of KIT mutations and can be associated with both mediator-related symptoms and organ dysfunction as a result of mast cell infiltration.[16] The WHO classification additionally categorizes systemic mastocytosis into a number of categories depending on the severity of the disease and its distinguishing features. The most common type is indolent systemic mastocytosis and is mild and does not result in severe organ damage and generally has a favorable prognosis. Smoldering systemic mastocytosis is considered an intermediate form, with a higher burden of mast cells and an increased risk of progression to a more aggressive disease.

More complex types are systemic mastocytosis associated with a hematologic neoplasm, where mastocytosis coexists with another hematological malignancy, e.g. leukemia or myeloproliferative disorders, and thus complicates the management of the disease. Aggressive systemic mastocytosis is characterized by extensive organ involvement, such as liver dysfunction, cytopenias, and malabsorption, due to widespread mast cell infiltration and is associated with a worse prognosis. Mast cell leukemia is a very rare and aggressive form characterized by the presence of large numbers of mast cells in the bone marrow and peripheral blood, and is often associated with a rapid disease

progression and poor clinical outcomes. There is also mast cell sarcoma which is an extremely rare, malignant type of mastocytosis where such tumors grow locally, but are highly destructive.[17]

The classification of mastocytosis is vital in the proper diagnosis and therapeutic decision-making. Since cutaneous mastocytosis is limited to the skin, it is mostly treated with topical and symptomatic therapies rendering it an ideal target of advanced topical drug delivery systems. Conversely, systemic mastocytosis should receive systemic and targeted therapeutic options because of its multiorgan involvement and the level of severity.

Cutaneous mastocytosis (CM) diagnosis is mainly through a combination of clinical examination, histopathological examination, and laboratory studies. CM is suspected when patients present with typical skin lesions including hyperpigmented macules, papules or plaques with symptoms such as pruritus, flushing, and urticarial.[18,19]

Diagnosis of Cutaneous Mastocytosis

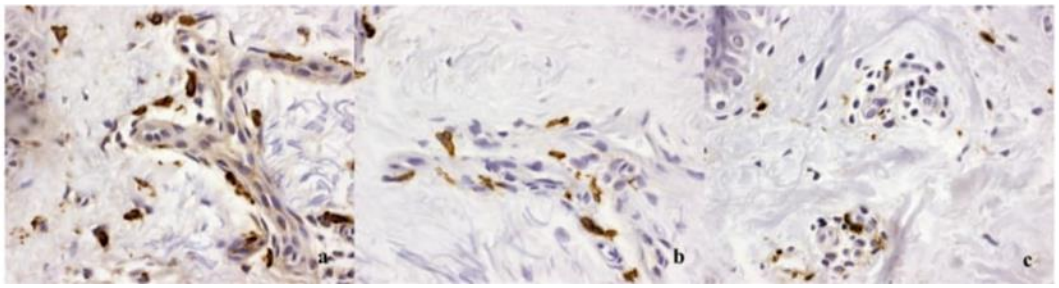

Fig. No. 3 Histopathology of a lesion from a patient with cutaneous mastocytosis may be diagnostic because of (a) a high number of mast cells in the dermis, but it may also be nondiagnostic, (b) showing not significantly increased mast cell numbers in comparison to (c) a control patient with atopic dermatitis and may require further criteria to be looked at. Tryptase stains at 40x.

Source: Brockow, Knut, et al. Diagnostics 14.2 (2024): 161

Diagnosis is definitively confirmed with skin biopsy which show that there are increased numbers of mast cells in the dermis. Mast cells are identified by using special stains like toluidine blue, Giemsa stain, or immunohistochemical markers, such as tryptase and CD117 (KIT). Besides that, serum tryptase levels could be obtained to measure the burden of the mast cell in purely cutaneous forms.[19]

More assessment is necessary to rule out systemic involvement especially in adult patients. This can incorporate bone marrow biopsy, imaging investigations, and molecular research of KIT mutations, particularly KIT D816V19.A thorough diagnostic method is therefore not only necessary to ensure CM but also to be able to distinguish between the two.

Cutaneous Mastocytosis: Need of Nanocarriers.

Cutaneous mastocytosis (CM) is a rare skin disease that is characterized by abnormal accumulation and activation of mast cells in the skin, resulting in symptoms such as pruritus, flushing, urtication, erythema, blisters, and inflammation. The traditional topical agents (such as corticosteroids, antihistamines, and calcineurin inhibitors) tend to demonstrate limitations such as lack of skin penetration, high dosage, local irritation, and inconsistent response to therapy. Thus, the nanocarrier-based Drug delivery system is a promising approach to enhance the management of CM.[32]

Nanocarriers which can be used to improve drug permeation through the stratum corneum and enhance localization of drugs within the epidermis and dermis which are mainly located in the mast cells. Such specific deposition can enhance therapeutic activity and decrease systemic exposure and side effects.[33]

The other beneficial requirement of nanocarriers in CM is the ability to control and sustain the release of anti-inflammatory, antihistaminic, or mast cell-stabilizing therapeutic agents. Long term drug release may decrease dosage, enhance patient compliance and offer long-term symptomatic relief to itching and irritation34.

Nanocarriers could also be used: to protect unstable drugs against degradation; to enhance the solubility of poorly water-soluble agents; and to enable combination therapy (co-loading of multiple drugs into a single carrier system). This holds especially in CM, where both mediator-release symptoms and inflammatory skin lesions could be requiring a combined treatment approach.[34]

Moreover, since CM often occurs in pediatric patients, less local therapy with minimal systemic absorption is very desirable. Topical delivery using nanocarriers may have a better safety profile than the long-term conventional topical corticosteroid therapy.[36]

To sum up, the application of nanocarriers in cutaneous mastocytosis is necessitated by the need to achieve better skin targeting, increased efficacy, sustained release, reduced side effects and enhanced patient compliance. Even though there are few direct clinical

studies in CM, present developments in dermatological nanomedicine indicate that in the future, there is potential to adopt a personalized and effective approach to the management of this rare disorder.[34]

Cutaneous Mastocytosis: Advanced Carrier / Nanocarrier Systems.

Cutaneous mastocytosis (CM) is a rare pathology that consists of excessive mast cell deposition in the skin, which leads to itching, erythema, flushing, urtication, blistering and inflammation. The traditional topical therapy usually exhibits a poor penetration through the stratum corneum, short residence time, frequent dosing and local adverse effects. Thus, innovative nanocarrier systems can deliver superior skin targeting and sustained release and improved therapeutic efficacy in CM. Though no nanocarrier system has been specifically commercialized to treat CM as yet, there are a number of advanced carriers in use to treat dermatological diseases that have a strong translational potential to treat CM.

1. Liposomes

Liposome are vesicles that are phospholipid bi-layers that are able to encapsulate both lipophilic and hydrophilic drugs. They also promote localization of drugs in stratum corneum and viable epidermis, reduce systemic absorption and might be useful in topical corticosteroids, antihistamines or mast cell stabilizers in CM39.

2. Transfersomes

Transfersome are very elastic vesicles which have the ability to squeeze through slender skin pores and penetrate deeper layers. Such systems have the potential to enhance the delivery of anti-inflammatory drugs to dermal mast cell infiltrates in CM40.

3. Ethosomes

Ethosomes have a high level of ethanol, which raises the flexibility of the vesicles and disrupts the lipid packing of the skin barrier, thus increasing dermal penetration. 40 Ethosomes are promising to increase the depth of skin deposition of anti-mast cell drugs.

4. Transethosomes

Transethosomes are ethanol-based liposomes that are combined with edge activators, which offer improved deformability and penetration over traditional liposomes. They may be useful in chronic or thickened CM lesions that need a deeper drug delivery.[41]

5. Solid Lipid Nanoparticles (SLNs)

Solid Lipid Nanoparticles offer control drug delivery, skin entrapment, increased hydration, and stability of drugs incorporated. SLNs can decrease applications and enhance compliance of patients in chronic CM therapy42.

Future Relevance in Cutaneous Mastocytosis.

With these advanced carriers, it may be possible to:

• Specifically directed to dermal mast cells.

• Prolonged liberation of antihistamines or corticosteroids.

• Lessened side effects on systems.

• Better infiltration into mast cell-laden layers of skin.

• Improved patient compliance and lower dosing schedule.

Potential multiple agents co-delivery within a single system[43].

Nanocarrier use in Cutaneous Mastocytosis.

Nanocarriers have become a promising modality of managing cutaneous mastocytosis (CM) due to its capacity to enhance topical drug delivery, enhance skin penetration, and provide sustained release of therapeutic agents. In CM, the mast cells predominantly accumulate in the epidermal and dermal layers; thus, localised delivery systems are very advantageous as compared to the traditional dosage forms.[51]

Lipid-based nanocarriers include liposomes, ethosomes, transfersomes, transethosomes, and solid lipid nanoparticles (SLNs), which can be effectively used as penetrating nanocarriers to deliver drugs to deeper skin layers. The systems can be used to administer antihistamines, corticosteroids, mast cell stabilizers, and anti-inflammatory agents directly to the site of lesion, thus minimizing adverse effects systemically.[53-54]

Nanogels and polymeric nanoparticles offer controlled and prolonged release of drugs, enhancing therapeutic efficacy and reducing the frequency of application. They are also able to stabilize sensitive drugs as well as improve patient compliance particularly in pediatric patients where CM is more prevalent.[55]

Topical delivery of poorly soluble or targeted drugs such as tyrosine kinase inhibitors (e.g., imatinib, midostaurin), which could be of use in treatment resistant or severe cases involving KIT mutations.[56]

Also, the treatment can be done using nanocarrier-based formulations to reduce skin irritation, increase hydration, and enhance cosmetic acceptability of treatment. Nanotechnology, in general, provides a contemporary platform of safer and more effective localized therapy in cutaneous mastocytosis.[57]

Cutaneous Mastocytosis Treatment.

Treatment of cutaneous mastocytosis is symptomatic in nature and is designed to address the release of mast cell mediators and it targets to enhance the quality of life of the patient. The first-line treatment normally involves the use of H1 antihistamines which are useful in reducing pruritus, flushing and urticaria through blocking of histamine receptors18. H2 antihistamines can be used in certain cases to help control the gastrointestinal symptoms of the mast cell mediator release.[20]

Topical therapies are important in the management of CM. Topical corticosteroids are often used in order to decrease inflammation and mast cell activity although such long-term use may cause adverse effects including skin atrophy19.Topical calcineurin inhibitors like tacrolimus and pimecrolimus have also been used as steroid-sparing agents with a good safety profile [2]. Mast cell stabilizers such as cromolyn sodium may also be used to help prevent the degranulation of mast cells as well as reduce the symptoms.[18]

Phototherapy, such as psoralen plus ultraviolet A (PUVA) and narrowband ultraviolet B (NB-UVB) may be used to decrease the number of mast cells and improve skin lesions in patients with more severe or refractory disease. In some specific instances, and especially where the symptoms are severe or unresponsive to standard therapy, advanced therapies such as omalizumab (anti-IgE monoclonal antibody) and tyrosine kinase inhibitors targeting KIT mutations are considered to be used in select cases.

In spite of these available therapies, CM treatment is still more symptomatic since no definite cure exists today. Hence, more attention is directed at innovative drug delivery methods especially nano-based topical systems to positively influence the therapeutic results.

Available Marketed Preparation

1) Topical corticosteroids

- Clobetasol propionate cream

Drawbacks :- cause skin atrophy,thinning, and stria with prolonged use [44]

- Betamethasone cream

Drawbacks :- cause hypopigmentation and skin irritation[45]

- Mometasone cream

Drawbacks :- possible burning , itching , irritation[46]

2) Antihistamines

A) H-1receptor blockers

- Doxepin

Drawbacks :- cause sedation and drowsiness,anticholinergic effects[47]

- Hydroxyzine

Drawbacks :- significant sedation affecting daily activities[49]

- Fexofenadin

Drawbacks :- less sedation but still may cause headache and dizziness[48]

B) H2 blockers

- Cimetidine

Drawbacks :- cause drug interactions, may lead to gynecomastia and hormonal imbalance

- Ranitidine

Drawbacks :- cause headache, GI disturbance[50]

Cutaneous Mastocytosis Treatment.

The treatment of cutaneous mastocytosis is more symptomatic and aims to regulate the release of mast cell mediators and enhance the quality of life of a patient. H1 antihistamines are normally used as first-line therapy to help in the reduction of pruritus,

flushing, and urticaria by blocking histamine receptors.[18] H2 antihistamines can also be used to treat gastrointestinal symptoms that release20 of mast cell mediators.

Topical treatment is an important aspect of CM management. Topical corticosteroids are widely used in the treatment of inflammation and mast cell activity although in long-term use there are some adverse effects associated with their application such as skin atrophy.[19] Steroid-sparing agents, which include the topical use of calcineurin inhibitors (tacrolimus and pimecrolimus) have also been used with good safety records.[2] Also, mast cell stabilizers such as cromolyn sodium may prevent mast cell degranulation and alleviate symptoms.[18]

Phototherapy, such as psoralen plus ultraviolet A (PUVA) and narrowband ultraviolet B (NB-UVB), may be used in patients with more severe or refractory disease, in order to help reduce the number of mast cells and improve skin lesions. In the application of advanced therapies, such as omalizumab (anti-IgE monoclonal antibody) and tyrosine kinase inhibitors targeting KIT mutations are considered in few cases, especially when the symptoms are severe or unresponsive to traditional treatment.[20]

Although these are the available therapies, CM treatment is most of the time symptomatic, since there is no definite cure of CM at the moment. As such, there is an increasing interest in advanced drug delivery methods, especially nano-based topical systems, to improve therapeutic outcomes.

Table 2. Treatment strategies in CM [4–7]

Signs and symptoms of cutaneous mastocytosis		First-line therapy	Other therapies	Prevention
Skin lesions	**MPCM/UP**	Short-term therapy with topical corticosteroids Treatment is not necessary in the majority of cases	Topical corticosteroids, UVA1, narrow-band UVB PUVA Pimecrolimus	Identification and avoidance triggers factors including the patients with IgE-mediated allergy
	DCM	Short-term therapy with topical and oral corticosteroids	UVA1 Narrow-band UVB PUVA	
	Mastocytoma	Without treatment or topical corticosteroids	Surgical excision Injection with crystalline steroid solutions Pimecrolimus	
Mast cell mediator-related symptoms	Tachycardia Hypotension Headache	Second-generation H1 antihistamines If symptoms persist, increase the dose up to 4 times	Adrenaline H2-antihistamines Oral glucocorticoids	–
	Pruritus Flushing Skin wheals		H2-antihistamines Leukotriene antagonist Disodium cromoglycate NSAID (if tolerance is known) Topical glucocorticoids PUVA UVA1 Narrow-band UVB	–
	Abdominal pain Nausea Diarrhea Duodenal ulcers		H2-antihistamines Proton pump inhibitors Oral disodium cromoglycate Oral glucocorticoids	–
Anaphylaxis		Emergency kit: 7.5 to 25 kg body weight: 0.15 mg adrenaline auto-injector ≥ 25 kg body weight: 0.3 mg adrenaline autoinjector H1, H2-antihistamines, glucocorticoids	Omalizumab in recurrent anaphylaxis SIT in Hymenoptera hypersensitivity	–

DCM – diffuse cutaneous mastocytosis, PUVA – UVA plus psoralen, NSAID – non-steroidal anti-inflammatory drugs, MPCM – maculopapular cutaneous mastocytosis, SIT – specific immunotherapy, UP – urticaria pigmentosa, UV – ultraviolet.

Table No. 2: Strategies in CM[4-7]

Source: Czarny, Justyna, et al. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii 35.6 (2018): 541-545.

Conclusion

To conclude, mastocytosis is a rare clonal disease that is marked by abnormal proliferation and accumulation of mast cells in different tissues with the skin being the most frequently affected organ. Even though the disease has various clinical manifestations, the majority of the cases have an indolent dlinical course. Developments of the molecular pathophysiology, especially the use of KIT (c-kit) mutations and normal mast cell immunophenotypes have contributed to significant improvements in the diagnostic and classification methods. Systemic involvement is more typical in adults and should be periodically assessed by bone marrow studies when the patient is suspected of having the disease. Early identification and proper diagnosis is vital to proper monitoring and management of the disease.

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