Rosacea: Update on Management and Emerging Therapies

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ABSTRACT

Rosacea is a common chronic skin disorder that has significant impact on the self-esteem and quality of life of affected individuals. Currently understood as an inflammatory condition that occurs in the context of an altered innate immune response, the available topical and systemic therapies function as immunomodulators to restore cutaneous homeostasis. The goals of therapy include reduction of papules, pustules, erythema and physical discomfort with improvement in quality of life. Standard topical treatments include metronidazole and azelaic acid, although many other agents and regimens have been presented. Subantimicrobial/anti-inflammatory dose oral doxycycline was US FDA approved in 2006 for the management of rosacea, but Health Canada clearance was only recently granted for this indication. Furthermore, renewed research interest has led to the development of other emerging therapies including topical ivermectin, brimonidine and oxymetazoline that hold promise for patients suffering from this condition.

Key words: erythema, inflammation, rosacea, telangiectasia

Introduction

Rosacea is a chronic skin disorder characterized by facial erythema, telangiectasia, inflammatory papules and pustules with intermittent episodes of exacerbation and remission. There are four generally accepted clinical subtypes, which have been described by the National Rosacea Society: erythematotelangiectatic, papulopustular, phymatous, and ocular.¹ Two variants, granulomatous and neurogenic, have also been presented.¹,² Affecting approximately 10% of the general population, rosacea is more prevalent in women, although impacted men often have more disfiguring skin changes.³ Patients often present between 30 and 50 years of age, but manifestations can occur throughout the life course.⁴ Given that up to a third of patients have a family history of rosacea and the increased prevalence among individuals of Northern European descent, an underlying genetic predisposition may help explain these patterns.⁵ While the etiology of rosacea remains unclear and despite clinical heterogeneity, basic science has developed a possible unified understanding of the condition as an inflammatory disorder in the context of an altered innate immune response.⁶ It is proposed that environmental changes, which may include UV light exposure, hormone balances, and microbe challenges (by pathogens such as Demodex folliculorum), are sensed by pattern recognition receptors of the immune system. Subsequent signaling-induced effector molecules such as reactive oxygen species, cytokines, cathelicidin and chemokines may then modify dermal structure through vascular changes, collagen degeneration, lymphohistiocytic infiltration and neutrophil recruitment, which may perpetuate this response.⁶,⁷ Given this model, it is clear why most current therapies attempt to modulate various points of this inflammatory cascade.

Furthermore, although the intricacies of the relationship between psychological factors and rosacea remains to be elucidated, 75% of affected patients report low self-esteem, with a significant odds ratio of 4.81 for a diagnosed depressive disorder in this population compared to the general population.⁸ The use of validated assessment tools has demonstrated the impact of rosacea on quality of life, and, importantly, the improvement in these psychological indices that can occur with treatment.⁹ Once rosacea is diagnosed, patients should be reassured of the benign, but chronic, nature of the condition. Counseling should be directed toward the identification and avoidance of triggers, diligent photoprotection, concealing cosmetics and proper skin care.³,¹⁰ It is also prudent to review medications to identify, and discontinue if possible, those that may exacerbate flushing such as beta blockers.³
**Treatment**

Topical pharmacotherapeutic options include azelaic acid, erythromycin, metronidazole or sodium sulfacetamide 10% + sulfur 5%. As in the management of other dermatological conditions, vehicle selection for topical rosacea preparations is an important consideration. The choice of lotion, cream, gel or foam can influence efficacy, compliance, and tolerability, which is especially relevant for these patients who often have heightened skin sensitivity, but is beyond the scope of this review. In patients with moderate to severe papulopustular subtype or ocular involvement, systemic therapy is often required and includes doxycycline, erythromycin, metronidazole, minocycline, tetracycline, or, in select severe cases, low-dose isotretinoin. Laser, light-based therapies and surgical interventions may also be warranted in select patient populations. Recent research has added low-dose doxycycline to the therapeutic armamentarium and two additional treatments, ivermectin and alpha-adrenergic receptor antagonists, hold promise for the future. This article will review the topical and systemic options for the management of cutaneous manifestations of rosacea with a focus on emerging therapies.

**Topical Metronidazole**

Topical metronidazole has been used in the treatment of rosacea since the 1950s. It has demonstrated greater efficacy compared to placebo in multiple trials with both statistically significant and clinically important results. There is no statistically significant difference between the two concentrations of topical metronidazole (0.75% or 1%) and it has also been shown to be effective in maintaining remission. Among available topical therapies metronidazole has also been proposed as the most cost-effective regimen, which may be an important consideration for some patients.

**Topical Azelaic Acid**

Azelaic acid is a naturally occurring saturated dicarboxylic acid approved for the treatment of mild to moderate rosacea. Patients using azelaic acid showed an improvement of 70-80% in their rosacea compared with 50-55% in the placebo group. Azelaic acid 15% gel administered once daily has demonstrated equivalent efficacy to twice daily application, although the recommended dosing is twice daily.

**Metronidazole versus Azelaic Acid**

In two studies comparing topical metronidazole and azelaic acid, there was no statistically significant difference between the treatment groups with respect to patient-assessed outcomes. However, in the split-face comparison clinical trial by Maddin, patients favored the outcome of azelaic acid. In both the Maddin and Elewski et al trials, the investigators were of the opinion that treatment with azelaic acid was more effective than metronidazole.

**Subantimicrobial Low-dose Oral Doxycycline**

Tetracyclines (pregnancy category D) have been a mainstay of rosacea therapy for more than half a century. However, a clear bacterial pathogen has not been implicated in the pathophysiology of rosacea. Furthermore, standard antimicrobial dosing may affect endogenous flora and risks the development of antibiotic resistant strains. Antibiotic stewardship is advocated in all medical disciplines in hopes of preserving efficacy for the management of bacterial infections. In light of these considerations, tetracyclines also have numerous anti-inflammatory properties thought to be responsible for their efficacy in the management of rosacea. They suppress neutrophil migration and chemotaxis, inhibit angiogenesis and the activation, proliferation and migration of lymphocytes, block production of matrix metalloproteinases (MMPs), and upregulate anti-inflammatory cytokines.

Anti-inflammatory, low-dose doxycycline 40 mg capsules, formulated as 30 mg immediate-release and 10 mg delayed-release beads and dosed once daily, provide a subantimicrobial dose that reduces the inflammatory response without producing drug concentrations required to treat bacterial diseases, thus avoiding concerns regarding selective pressures generating microbial resistance. The efficacy of oral doxycycline 40 mg capsules once daily in the treatment of adults with rosacea was demonstrated in two large, randomized, double-blind, placebo-controlled, multicenter trials. Assessed after 16 weeks of therapy, doxycycline 40 mg provided a significantly greater reduction in the total inflammatory lesion count (primary endpoint) than placebo. Furthermore, doxycycline 40 mg was associated with a rapid onset of action, with a significantly greater decrease in lesion count than placebo by first follow-up at 3 weeks in both studies. Interestingly, maximum anti-inflammatory effects appear to be achieved with doxycycline 40 mg capsules once daily. In a small, randomized, double-blind trial, no additional improvement in rosacea symptoms was achieved with oral doxycycline 100 mg once daily. The treatment was generally well-tolerated by patients; adverse events (experienced by approximately 4% of patients) were of mild to moderate intensity, with headache, nasopharyngitis and gastrointestinal side effects reported most frequently. No photosensitivity was observed, although tetracyclines as a class of medications have been associated with this effect. Doxycycline 40 mg capsules have been demonstrated as safe and effective monotherapy for rosacea in both males and females and in patients of all skin types. Furthermore, patient-rated measures report improvement in symptoms, reduction in the interference of symptoms with life activities, and satisfaction with treatment. Combination therapy with doxycycline 40 mg plus either azelaic acid gel 15% or metronidazole gel 1% were also safe, efficacious and well-tolerated.

**Emerging Therapies**

**Ivermectin cream (CD5024)**

An agent currently under investigation is CD5024 1% cream, which is a new topical formulation of the acaricidal compound, ivermectin. Although the exact pathophysiology is yet to be elucidated, one well-known hypothesis for the etiology of rosacea is the presence of Demodex mites in the pilosebaceous unit of affected individuals. Reports have been published on cutaneous demodiosis responding to oral ivermectin and topical permethrin, but data is lacking on the topical application of ivermectin alone.

There are currently three Phase III studies ongoing, one comparing CD5024 1% cream to metronidazole cream 0.75% (ClinicalTrials.gov identifier NCT01493947) and two similar studies comparing CD5024 1% cream to azelaic acid 15% gel.
with an initial randomized controlled phase for 12 weeks, and a comparator extension phase for 40 weeks (ClinicalTrial.gov identifiers NCT01494467 and NCT01493687). The projected trial completion date is August 2013.

**Adrenergic Receptor Antagonists: Brimonidine and Oxymetazoline**

Novel therapies to treat the erythema associated with rosacea are under development and have the potential to fill a void in the arsenal of rosacea therapeutics. The adrenergic receptor antagonists brimonidine tartrate and oxymetazoline, which have potent vasoconstrictive activity and anti-redness capabilities, are currently found in eye drops for glaucoma and a nasal decongestant spray, respectively.38 Results of the Phase II study to be safe and efficacious in reducing the erythema of rosacea. A single application of the 0.5% gel reduced erythema between 30 minutes to 12 hours, as measured with an objective chromameter.39 In part B of the study, two dosages (0.18% and 0.5%) of the gel was compared to vehicle over a 4 week period in 269 subjects. No tachyphylaxis, aggravation of symptoms or rebound erythema was observed. The majority of adverse effects were skin-related and mild and transient in nature. The 0.5% gel once daily was significantly more effective according to both patient and clinician assessments (≥ two-grade improvement) and is the dose that has gone forward in Phase III clinical development to confirm safety and efficacy.38 Results of the Phase III randomized controlled trials are anticipated to be released in the fourth quarter of 2012.

Oxymetazoline or AGN-199201, a potent alpha-1 and partial alpha-2 receptor agonist, has been shown in case reports to be as effective as metronidazole 1% cream.49 It has been formulated into a cream and is currently in clinical development for the treatment of erythematotelangiectatic rosacea (ClinicalTrials.gov identifier NCT 01579084).41

**Other Treatments**

- Available for more than 50 years, topical sodium sulphacetamide 10% + sulphur 5% has also been demonstrated to significantly reduce inflammatory lesions and facial erythema compared to vehicle.42 However, the quality of studies evaluating this therapy have been generally poor.14
- Systemic isotretinoin has also been used off-label in the treatment of patients with severe rosacea. A randomized, double-blind, non-inferiority trial comparing the use of different dosages of oral isotretinoin to both doxycycline or placebo found isotretinoin 0.3 mg/kg to be an effective agent for reducing facial erythema.40 It has been formulated into a cream and is currently in clinical development for the treatment of erythematotelangiectatic rosacea (ClinicalTrials.gov identifier NCT 01579084).41
- Various topical regimens including an antibiotic and retinoid preparations have been proposed. A recent randomized, double-blind, placebo-controlled study assessing a combination gel of clindamycin phosphate 1.2% + tretinoin 0.025% found no difference in papule/pustule count, but mild improvement in the telangiectatic component of rosacea was observed.44
- Although not FDA approved for the management of rosacea, a randomized, double-blind, vehicle-controlled trial has demonstrated the efficacy of once daily topical benzoyl peroxide 5%/clindamycin 1% gel in patients with moderate to severe rosacea.45 Common adverse events include pruritus, burning, and bleaching of hair/clothing.

- In a randomized, controlled, single-blind, split-face trial of patients with erythematotelangiectatic rosacea, both pulsed dye laser and intense pulsed light treatments were found to have similar efficacy and safety.46,47
- An open-label uncontrolled trial of the calcineurin inhibitor pimecrolimus 1% cream suggests it is effective and well-tolerated for mild to moderate inflammatory rosacea.48 A small, single-centre randomized study found pimecrolimus 1% cream to be as effective as metronidazole 1% cream.49
- The use of oral zinc sulfate has also been proposed for the management of rosacea. However, a randomized, double-blind trial of 220 mg zinc sulfate dosed twice daily showed no difference in magnitude of improvement between subjects receiving zinc therapy versus placebo.50
- Due to the chronic nature of the condition, patients frustrated with medical therapy may turn to marketed botanicals and herbal remedies in hopes of improved control. Although there is a paucity of data surrounding the effects of these cosmeceuticals, the prudent clinician should be aware of products that may be used by patients such as niacinamide, feverfew, turmeric, colloidal oatmeal and quassia extract.51,52

**Conclusion**

With the advent of novel therapeutic options for the treatment of rosacea such as subantimicrobial anti-inflammatory dose doxycycline, ivermectin and the alpha-adrenergic receptor antagonists, there is renewed interest in the study of this chronic inflammatory condition. There is ongoing need for well-designed, high-quality studies of widely used treatments for rosacea including isotretinoin, sodium sulphacetamide/sulphur, and light-based therapies, as well as comparative studies, given the emergence of new treatments. Lifestyle interventions such as avoidance measures for triggering factors, the use of sunscreen, dietary changes and patient education are additional areas of needed research. It would be beneficial for outcomes in future trials to be based on validated, standardized scales assessing both efficacy and improvement in quality of life. Where possible, therapeutic decision-making should take into account high-level evidence and be guided by clinical experience, individual patient characteristics and preferences until further evidence is available.

**References**


A Practical Approach to Accurate Classification and Staging of Mycosis Fungoides and Sézary Syndrome

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ABSTRACT

Cutaneous T-cell lymphomas are rare, distinct forms of non-Hodgkin's lymphomas. Of which, mycosis fungoides (MF) and Sézary syndrome (SS) are two of the most common forms. Careful, clear classification and staging of these lymphomas allow dermatologists to commence appropriate therapy and allow correct prognostic stratification for those patients affected. Of note, patients with more advanced disease will require multi-disciplinary input in determining specialist therapy. Literature has been summarized into an outline for classification/staging of MF and SS with the aim to provide clinical dermatologists with a concise review.

Key words: CTCL, cutaneous T-cell lymphoma, mycosis fungoides, neoplasm staging, Sézary syndrome, therapy

Primary cutaneous lymphomas (PCL) are rare forms (2%) of non-Hodgkin’s lymphomas with an annual incidence of 0.3-1 per 100,000.¹ These lymphomas include both primary cutaneous T-cell (75%) and B-cell lymphomas defined by presentation at the time of diagnosis without any extracutaneous sites of disease.³ In 2005, the two classification systems for cutaneous T-cell lymphoma (CTCL), namely the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC), were combined, providing distinct subtypes based on clinico-pathologic criteria (Table 1).¹,²

Mycosis fungoides (MF) represents the most common variant of CTCL³ and is characterized by a monoclonal proliferation of epidermotropic CD4+/CD45RO+ T-cells often with aberrant expression of mature T-cell antigens.¹,⁴ MF (Alibert-Bazin type) is characterized by the presence of polymorphic patches, plaques, and tumors.¹ Sézary syndrome (SS) is a rare CTCL variant closely related to MF and has classically been described as a triad of erythroderma, generalized lymphadenopathy and Sézary cells (atypical neoplastic T lymphocytes with hyperconvoluted cerebriform nuclei) in the skin, blood, and lymph nodes.¹,³,⁵ The WHO-EORTC system currently distinguishes SS as a separate entity from MF, but rare cases of SS preceded by typical MF have been described.³,⁷

Table 1: WHO-EORTC classification of cutaneous lymphoma with primary cutaneous manifestations¹

<table>
<thead>
<tr>
<th>Classification</th>
<th>Cutaneous T-cell and NK-cell lymphomas</th>
<th>Mycosis fungoides</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF variants and subtypes</td>
<td>• Folliculotropic MF</td>
<td>Pagetoid reticulosis</td>
</tr>
<tr>
<td></td>
<td>• Granulomatous slack skin</td>
<td></td>
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<tr>
<td>Sézary syndrome</td>
<td></td>
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<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td></td>
<td></td>
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<tr>
<td>Primary cutaneous CD30+ lymphoproliferative disorders</td>
<td>• Primary cutaneous anaplastic large cell lymphoma</td>
<td>Lymphomatoid papulosis</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous peripheral T-cell lymphoma, unspecified</td>
<td>• Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)</td>
<td>Cutaneous gamma/delta T-cell lymphoma (provisional)</td>
</tr>
<tr>
<td></td>
<td>• Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)</td>
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</table>

Cutaneous B-cell lymphomas

Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other

Precursor hematologic neoplasm
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

Table 1: WHO-EORTC classification of cutaneous lymphoma with primary cutaneous manifestations¹
In this article, we will focus primarily on the evaluation and classification of these conditions and summarize the available therapies.

### Evaluation

A confident diagnosis of MF can only be made from a combination of clinical and pathologic findings. Characteristic pathologic features include cytologically atypical lymphocytes with cerebriform nuclei (described above) either colonizing the basal layer of the epidermis (epidermotropism) or forming clusters of cells in the epidermis (Pautrier microabscesses) with or without a band of cytologically atypical cells in the upper dermis.\(^1,^8,^9\) An algorithm for the diagnosis of early-stage MF has been suggested by the International Society of Cutaneous Lymphoma (ISCL), which includes clinico-pathological correlation and immunophenotypic and clonal T-cell receptor gene rearrangement studies, providing minimum criteria for diagnosis (Table 2).\(^2,^8\) For SS, ISCL recommends the presence of erythroderma and the demonstration of the same T-cell clone (using polymerase chain reaction [PCR] or Southern blot of the T-cell receptor [TCR] gene) in skin and blood plus one of the following: Sézary cell count >1000 cells/mm\(^3\); expanded CD4+ population with CD4/CD8 ratio >10; or loss of T-cell antigens (CD2, CD3, CD4, CD5 and CD7).\(^1\) It must be appreciated that the diagnosis of early MF can be difficult and repeated biopsies may be required.\(^2,^8\) Careful clinico-pathological evaluation with a dermatologist and experienced pathologist in PCLs is recommended (Table 3).

### Table 2: An algorithm for diagnosing early MF* (ISCL)\(^2,^3\); * A total of 4 points is required to make a diagnosis of MF

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Scoring*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Essential</td>
</tr>
<tr>
<td>Persistent and/or progressive patches/thin plaques</td>
<td>1. Non-sun exposed location</td>
</tr>
<tr>
<td><strong>Histopathologic</strong></td>
<td>Superficial lymphoid infiltrate</td>
</tr>
<tr>
<td><strong>Molecular biological</strong></td>
<td>Clonal TCR gene rearrangement</td>
</tr>
<tr>
<td><strong>Immunopathologic</strong></td>
<td>1. CD2+, CD3+ and/or CD5+ &lt;50% of T cells</td>
</tr>
</tbody>
</table>

### Table 3: Evaluation/staging of patients with MF/SS\(^2,^3\); CBC = complete blood count; FDG-PET = fluorodeoxyglucose-positron emission tomography; FNA = fine-needle aspiration; TCR = T-cell receptor

<table>
<thead>
<tr>
<th>Evaluation/Staging</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical exam</strong></td>
<td>Skin lesions</td>
</tr>
<tr>
<td>• If patch/plaques or erythroderma: determine percentage of body surface area and note any ulceration</td>
<td></td>
</tr>
<tr>
<td>• If tumors: note the total number, largest lesion, and regions affected</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></td>
<td>Note: if &gt;1.5 cm or firm, irregular, clustered, or fixed</td>
</tr>
<tr>
<td><strong>Organomegaly</strong></td>
<td>Present/not present</td>
</tr>
<tr>
<td><strong>Skin biopsy</strong></td>
<td>Site</td>
</tr>
<tr>
<td>• Most indurated area and compare plaques to tumors</td>
<td></td>
</tr>
<tr>
<td>• The site should be free from topical steroid for at least 2 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Tests</strong></td>
<td>• Immunophenotyping for CD2/3/4/5/7/8 and B-cell markers such as CD20, CD79a, as well as other markers such as CD56 and Ki67 may be indicated</td>
</tr>
<tr>
<td>• TCR gene analysis for clonal TCR gene rearrangements</td>
<td></td>
</tr>
<tr>
<td><strong>Bloods tests</strong></td>
<td>• CBC, liver function tests, LDH and chemistries</td>
</tr>
<tr>
<td>• TCR gene analysis - to compare with tissue biopsy</td>
<td></td>
</tr>
<tr>
<td>• Analyze any abnormal lymphocytes - Sézary cell count and/or flow cytometry (CD4+/CD7- or CD4+/CD26-)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td>• Chest X-ray in T1-2N0B0 with limited skin involvement and no organ specific complaints</td>
</tr>
<tr>
<td>• CT scan of chest, abdomen, and pelvis for all other groups. Role of FDG-PET scan has yet to be defined</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph node biopsy</strong></td>
<td>Which node? Excision biopsy or core biopsy preferred to FNA</td>
</tr>
<tr>
<td>• If nodes &gt;1.5 cm or firm, irregular, clustered, or fixed</td>
<td></td>
</tr>
<tr>
<td>• Choose largest node draining an involved area or the node with the highest standardized uptake value from FDG-PET scan</td>
<td></td>
</tr>
<tr>
<td><strong>Tests</strong></td>
<td>• Light microscopy/immunophenotypic studies/TCR gene analysis</td>
</tr>
</tbody>
</table>
**Prognosis**

The prognosis of MF/SS is primarily based on stage, particularly the extent/type of lesions and presence of extracutaneous disease,\(^2\) emphasizing the importance of thorough patient work-up. Of note, MF/SS are thought as incurable diseases but the majority of patients with MF have an indolent disease course with 65-85% of patients being stage IA or IB at diagnosis.\(^2\)\(^,\)\(^12\)\(^-\)\(^14\) Patients with stage IA disease have a median survival of more than 12 years and no decrease in survival when compared to an age-, sex- and race-match control population.\(^1\)\(^,\)\(^2\)\(^,\)\(^15\)\(^-\)\(^17\) It is now appreciated that for patients with stage IB, the presence of plaques (\(T2_b\)) is associated with a worse prognosis and increased risk of disease progression when compared to those with only patches (\(T2_a\)).\(^12\) In contrast, patients with more advanced stage disease (stages IIB, III, IVA) have a median survival of 5 years and stage IVB patients have a median survival of 2.5 years.\(^2\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^15\)\(^,\)\(^17\) More specifically, patients with dermatopathic nodes (N1) also have a poorer survival when compared to those with no palpable nodes (N0). The presence of abnormal nodes with no histological confirmation (Nx) also have a mortality/poor outcome.\(^14\) A recent study also showed that patients with stage B0b (<5% Sézary cells with a T-cell clone) have a significantly worse overall and disease-specific survival with an increased risk of progression when compared to B0a (without a T-cell clone). A comparison study between stages B1 and B2 showed no significant difference in survival outcomes (Table 6).\(^14\)

### Classification/Staging

The management of MF/SS is a stage-based approach derived from the TNM (tumor-node-metastasis) Classification of Malignant Tumours (Table 4). Patients with Stage IA, IB or IIA have an early stage disease compared to IIB (tumor), III (erythroderma), and IV (pathologically involved nodes - IVA; visceral involvement - IVB) have advanced-stage disease (Table 5).\(^2\) Of note, there are two main classifications for lymph node involvement. The Dutch system defines atypical cells as cerebriform cells with a diameter >7.5 µm - increasing grade is associated with increased involvement of these cells.\(^10\) The second system, the National Cancer Institute and Veteran's Administration Hospital (NCI-VA) classification focuses primarily on the number of cells within the paracortex of the lymph node and their subsequent effect on the structure of the node.\(^11\)

### Limited-stage Disease

| IA | T1, N0, M0, B0-1 |
| IB | T2, N0, M0, B0-1 |
| IIA | T1-2, N1-2, M0, B0-1 |

### Advanced-stage Disease

| IIB | T3, N0-2, M0, B0-1 |
| IIA | T4, N0-2, M0, B0 |
| IVA | T4, N0-2, M0, B1 |
| IVA | T1-4, N0-2, M0, B2 |
| IVB | T1-4, N3, M0, B0-2 |

### Table 4: Classification of MF/SS (ISCL/EORTC revision)\(^2\)\(^,\)\(^3\)\(^,\)\(^10\)\(^,\)\(^11\)

\(^*\) Patches are without elevation or induration; + National Cancer Institute and Veteran's Administration Hospital classification

### Table 5: Staging of MF/SS (ISCL/EORTC revision)\(^2\)\(^,\)\(^3\)

T1-4: tumor stage; N0-3: nodal stage; M0-1: visceral organs; B1-2: peripheral blood

### Prognosis

The prognosis of MF/SS is primarily based on stage, particularly the extent/type of lesions and presence of extracutaneous disease,\(^12\) emphasizing the importance of thorough patient work-up. Of note, MF/SS are thought as incurable diseases but the
Table 7: Summary of therapies available for MF/SS2,19; + = frequency of use; * Refer to National Cancer Center Network and EORTC consensus recommendations for further guidelines and information regarding therapy for MF/SS; ** Active surveillance - reviewing at regular intervals and reserving treatment for disease-related symptoms; EMA = European Medicines Agency

Table 6: Prognostic characteristics in MF/SS defined from a cohort of 1,502 patients

OS = overall survival; DSS = disease-specific survival; RDP = risk of disease progression

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Better OS, DSS or decreased RDP</th>
<th>Worse OS, DSS or increased RDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td>Advanced clinical stage; increased age; male sex; increased LDH; large-cell transformation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypopigmented MF; MF with lymphomatoid papulosis; poikilodermatous MF;</td>
<td>OS and RDP</td>
</tr>
<tr>
<td></td>
<td>Folliculotropc MF</td>
<td>RDP only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td>Advanced skin (T) stage; blood stage B0b (blood clone without Sézary cells); increased LDH; folliculotropc MF</td>
<td>OS, DSS and RDP</td>
</tr>
<tr>
<td></td>
<td>Large-cell transformation</td>
<td>RDP only</td>
</tr>
<tr>
<td></td>
<td>Advanced N, M and B stages; increased age; male sex</td>
<td>OS and DSS</td>
</tr>
</tbody>
</table>

Treatment

Successful treatment of MF/SS requires appropriate classification/staging, multi-disciplinary input and personalized patient therapy (including age, co-morbidities, and performance status). Treatment should be focused on trying to induce sustained remission as measured by tumor burden. At present, there are no curative therapies and sometimes palliative options are the only appropriate therapeutic intervention with maintenance of a patient’s quality of life. The standard approach for early stage disease is skin-directed therapy including topical agents.
phototherapy, and radiotherapy. Long-term durable remissions are rare. Total skin electron beam (TSEB) therapy and immunobiologics are key options for patients with disease that is resistant to skin-directed treatments. Patients in advanced disease stages often receive chemotherapy but responses are rarely sustained. Several novel agents such as fusion toxins (denileukin diftitox), bexarotene, and histone deacetylase (HDAC) inhibitors have received US FDA approval during the last few years and offer promising alternatives to chemotherapy. Similarly, data on antibodies such as alemtuzumab suggests significant and occasionally durable responses. Table 7 summarizes many of the available therapies.

**Conclusion**

Appropriate therapy for advanced stages of MF/SS can only be initiated based on a multi-disciplinary approach (including dermatologists, pathologists, and oncologists) to classification and staging. Accurate staging and work-up will allow appropriate therapy and prognostic details to be delivered to each individual patient.

**References**

The US FDA approved a poly-ureaurethane 16% nail solution in September 2012 for the management of fragile, damaged or brittle nails with cracking or splitting (referred to as nail dystrophy). Among the most common forms of nail dystrophy is brittle nail syndrome, which affects about 20% of the general population. Symptoms include painful nails that can interfere with daily activities (e.g., negatively impact occupational abilities). This novel formulation mechanically supports the damaged nail plate using a proprietary polymer blend that creates a strong adhesion to the nail surface, forming a barrier that protects from further injury and strengthens the nail.

The FDA approved a supplemental New Drug Application (sNDA) in September 2012 for calcipotriene foam 0.005%. Approval of this sNDA expanded the sanctioned uses to include the topical treatment of plaque psoriasis of the scalp. With these recent changes, this topical synthetic vitamin D3 analog is now indicated for the treatment of plaque psoriasis of the scalp and body in patients >18 years of age.

The FDA granted an additional indication in August 2012 to this transparent hyaluronic acid gel dermal filler. The expanded indication includes submucosal implantation for lip augmentation in patients >21 years of age. Restylane-L® is also approved for injection into facial tissue to smooth wrinkles and folds (e.g., nasolabial). The gel temporarily adds volume to the skin and can give the appearance of a fuller lip or a smoother surface. This formulation contains 0.3% lidocaine, a topical anesthetic intended to reduce pain experienced by patients during the procedure.

In September 2012, the FDA issued a warning letter to Lancôme USA, a unit of L’Oréal SA, regarding the marketing of certain anti-wrinkle products, saying the products are promoted with claims and language suggestive of drugs. The letter specifically cited examples from the manufacturer’s website, including Lancôme’s Génifique Youth Activating Concentrate, Génifique Eye Youth Activating Eye Concentrate, and Génifique Cream Serum Youth Activating Cream Serum with the claim "Boosts the activity of genes and stimulates the production of youth proteins; Génifique Repair Youth Activating Night Cream Boosts the activity of genes; and Absolue Eye Precious Cells Advanced Regenerating and Reconstructing Eye Cream and Absolue Night Precious Cells Advanced Regenerating and reconstructing Night Cream claim to contain A powerful combination of unique ingredients – Reconstruction Complex and Pro-Xylane™, a patented scientific innovation – has been shown to improve the condition around the stem cells and stimulate cell regeneration to reconstruct skin to a denser quality.” The FDA states any product that is intended to affect the structure or function of the human body is classified as a drug and companies are prohibited from the sale of such products in the US without submitting an application to the agency proving safety and efficacy prior to being granted marketing approval. The current wording of the claims promotes therapeutic properties that cause the cosmeceutical products to be considered as drugs, therefore violating the Federal Food, Drug, and Cosmetic Act. More information is available at: http://www.fda.gov/ICECI/EnforcementActions/WaringLetters/2012/ucm318809.htm