Management Strategies for Mycosis Fungoides in India
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Abstract
Mycosis fungoides is the most common primary cutaneous T-cell lymphoma. The approach to diagnosis and further follow-up is outlined. Evidence for interventions is based classically on a Tumor Node Metastasis Blood TNMB “stage-based” approach. The treatment options in India are limited. The options as per risk stratification and prognostic index are discussed. Early stages and low-risk patients can be managed with expectant policy or skin-directed therapies including topical steroids and phototherapy; intermediate-risk patients can be opted for interferons or retinoids or low dose methotrexate along with radiotherapy including total skin electron beam therapy while high-risk patients are managed most often with single agent or multiagent palliative chemotherapy. Patients who are intermediate- or high-risk need management by a multispecialty team at tertiary care centers.

Key Words: India, large cell transformation, mycosis fungoides, prognosis, risk stratification, treatment

Introduction
Primary cutaneous lymphomas are rare extranodal lymphomas defined by specific clinicopathologic features,[1] the most common being mycosis fungoides (MF).[2] The National Comprehensive Cancer Network,[3] the European Organization for Research and Treatment of Cancer (EORTC),[4] European Society for Medical Oncology,[5] and the Japanese Skin Cancer Society – Lymphoma Study Group[6] have guidelines for management, but the rarity of patients in the Indian setting and unavailability of specific drugs make treatment not standardized in the absence of resources. There is also a paucity of data globally on randomized controlled trials in available options for therapy.

The management approach is often multidisciplinary though the initial presentation is most commonly to a dermatologist. Two-thirds of all cutaneous lymphomas are MF[7] in India, so we shall restrict to the management of this particular condition only.

In this article, we discuss the approach, investigations, and treatment options available as of now in India [Table 1].

Diagnosis
The diagnosis of MF is based on set clinicopathologic criteria. Consensus approach of early-stage MF has been proposed by the International Society of Cutaneous Lymphoma (ISCL),[1] and an updated staging system proposed by the ISCL/EORTC[8] has been adopted by the American Joint Committee on Cancer.

A majority of patients present with clinical Stage IA–IB without palpable lymphadenopathy, and their investigative work-up is limited.[2] Nevertheless, about 25% can have progressive disease.[9] The management is stage based, and the prognosis varies greatly in low-risk (Stage 1A), intermediate-risk (Stage 1B–2A) and high-risk cases (Stage 2B–4B).[9-15]

An algorithmic stage-based management strategy for available options is demonstrated [Figure 1]. However, there are factors besides the TNMB stages that can be important for prognosis and choice of therapy.[11]

Large cell transformation (LCT) can occur in early or late MF.[14] This is one of the reasons for follow-up biopsies and a definitive indication for biopsies in sudden clinical progression. The presence of CD30+ is not necessarily LCT. LCT is defined as the presence of large cells (≥4 times the size of a small lymphocyte) in >25% of the infiltrate or these large cells forming microscopic nodules.[16] LCT marks an aggressive disease and sometimes, resistance to
chemotherapy. Palliative radiotherapy is an option in these patients.

An objective way of clinical assessment can be done by the modified severity weighted assessment score (Cutaneous Lymphoma Resource Tools app). A prognostic index can be thereafter used to assess risk and prognosticate survival [Table 2].

**Low risk**
Patch stage MF with <10% BSA involvement poses a low risk. Hypopigmented MF in adolescents is a classic example. The risk of progression is so low that a school of thought exists to club these as hypopigmented dermatosis and manage them with no active intervention and only clinical follow-up.

Few patch stage lesions can be managed with topical mid-potent steroids with or without phototherapy such as narrow band ultraviolet B (UVB) or psoralen plus ultraviolet A (PUVA) or PUVAsol in India. These patients form a majority, especially in children and young adults who are diagnosed with MF. Hypopigmented MF which needs to be differentiated from vitiligo can be treated on similar lines of management with remission that lead to delayed diagnosis since both respond excellently to topical steroids and phototherapy. A single patch/plaque, although rare, can be subjected to radiotherapy with expected complete response of up to 100%.

**Intermediate risk**
These situations warrant multiple skin-directed and systemic treatment interventions. Maintenance treatment for these situations is guided by the poor prognostic factors in MF [Table 2].

### Table 1: Options available for management in India

| Options                  | Comments                                                                 |
|--------------------------|---------------------------------------------------------------------------|
| Wait and watch           | Only for Stage 1A. In children or single/limited patches, nonprogressive |
| Topical steroids         | Low or mid-potent steroids, simple to use. Long-term and extensive use associated with cutaneous adverse effects such as atrophy. Useful in early stages |
| PUVA - bath PUVASol, PUVA, chamber PUVA | For patch/plaque stage. Combined with acitretin, interferons. Can be used for maintenance. 2/3 times/week. Cumulative toxicity and risk of malignancy for prolonged therapy |
| NB-UVB                   | Patch stage disease. Safer in children                                 |
| Imiquimod                | For smaller lesions and few lesions. Can cause inflammatory reactions   |
| Acitretin                | Used since bexarotene not available, durability limited                  |
| Interferon alpha         | Good results in plaque stage and beyond with combined phototherapy. Tolerance and compliance poor as daily/thrice weekly injections. Expensive monitor counts and thyroid function |
| Methotrexate             | Weekly convenient oral dosing. Dose-response effect good at 20-30 mg/week. Cytopenia and liver function monitoring needed. Combination with other therapies useful |
| Localized radiotherapy   | For localized lesions or sanctuary sites. Response good                 |
| TSEB                     | Low dose TSEB better tolerated. Can be repeated. Available at select centers |
| Systemic chemotherapy    | Beyond second line, in refractory disease. Remission period short. Follow-up with skin-directed therapies. Cytopenia common |
| (doxorubicin, gemcitabine, CHOP) |                                                                       |
| Allogenic transplant     | In select patients only                                                  |

TSEB: Total skin electron beam, PUVA: Psoralen plus ultraviolet A, NB: Narrowband, UVB: Ultraviolet B, CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisolone

### Table 2: Poor prognostic factors in mycosis fungoides

| MF                              | Variables                                                                 |
|---------------------------------|---------------------------------------------------------------------------|
| Early stage                     | Plaque                                                                    |
|                                 | Folliculotropic                                                          |
|                                 | Male                                                                      |
|                                 | Age >60                                                                   |
|                                 | N1/Nx stage for nodal involvement                                        |
| Late stage                      | Male                                                                      |
|                                 | Age >60                                                                   |
|                                 | N2/N3 stage of nodal involvement, B2/B3                                   |
|                                 | blood involvement, visceral involvement                                   |

Large cell transformation itself is not a poor prognostic factor: When associated with advanced stage at transformation, extracutaneous transformation like in nodes, CD30 negativity, folliculotropic MF, and increased extent of skin lesions in the presence of LCT are markers of poor prognosis. LCT: Large cell transformation, MF: Mycosis fungoides, early stage: TNMB Stage 1A-2A, Late stage: TNMB 2B-4B

Figure 1: Algorithm mycosis fungoides
systemic treatment may be necessary in early-stage disease if there is no sustained response to skin-directed treatment.\(^\text{(23)}\)

UVA induces better response rates compared to UVB in plaque stage disease, with complete remissions reported up to 58\% in patch stage disease.\(^\text{(21,24)}\) However, although PUVA phototherapy is effective, durable complete responses are rare. There is a theoretical risk of skin cancers such as squamous cell carcinoma if the total lifetime cumulative UVA dose should exceed 1000 J/cm\(^2\) or 250 sessions.\(^\text{(25)}\) There have been no reports from India of PUVA-induced malignancy in this subset of patients. UVB phototherapy has a better safety profile than PUVA and should be preferred in patients with predominant patches. PUVA would be an alternative if there is a suboptimal response or patients with extensive thick plaques.\(^\text{(26)}\)

The combination of PUVA and interferon-alpha (IFN-\(\alpha\)) or bexarotene has been studied.\(^\text{(27,28)}\) Since bexarotene is not available in India, combination with acitretin has been tried with variable results.\(^\text{(29)}\) Our center experience (unpublished data) shows a partial response rate of 70\% but not durable with UVA combined with acitretin.

Bexarotene and IFN-\(\alpha\) have reported comparable results.\(^\text{(30)}\) IFNs given daily or thrice weekly at 3–9 million unit should only be considered as a second-line therapy for early-stage disease. While pegylated IFN-\(\alpha\) has a more convenient weekly dosing, the efficacy might be the same.\(^\text{(31)}\)

Low-dose methotrexate (MTX) can be a choice for patients with early stages of MF if disease is resistant to skin-directed therapies. Doses can range between 25 and 75 mg/week. Complete remission rates are as low as 12\% with a median of 15 months for treatment failure in reported data.\(^\text{(31)}\) Low-dose MTX has also been successfully combined with IFN-\(\alpha\).\(^\text{(32)}\)

Cutaneous lymphomas are extremely radiosensitive. Therefore, radiotherapy is a preferred palliative option for MF, especially for sanctuary sites resistant to phototherapy.\(^\text{(21,22,33)}\) In most instances, the target volume is the epidermis and/or dermis, except those with tumors or deep ulcers. Hence, lesions can be treated with soft (low penetrance) beam–superficial radiograph therapy (50–145 peak kV) or 4–9 MeV electron beams. For thicker lesions, higher energy of radiotherapy can be opted.

Total skin electron beam (TSEB) therapy is an excellent treatment option for MF with a high rate of complete remissions. In TSEB therapy, the patient is exposed to either multiple field arrangements or a rotational technique (Stanford technique), with “patching” or “boosting” for areas of underdosing and self-shielding (e.g., soles of feet and perineum). The full dose regimen takes 6–10 weeks to complete. This option of management is available at selected centers in India allowing patients to benefit from TSEB.

Previously, the cutaneous toxicity from TSEB at high doses (30–36 Gy in 20–36 fractions) was a limiting factor. Now, several centers have demonstrated comparable remission rates with low-dose regimens (10–12 Gy in 8–12 fractions).

Although with low-dose TSEB, the CR rates are lower; this choice of therapy is better because repeat courses are better tolerated and can provide excellent palliation. Follow-up treatment in intervals can be with PUVA +/- interferons/acitretin.\(^\text{(6,22,24)}\)

**High risk**

These patients present with erythroderma and blood or nodal involvement. Erythrodermic MF is encountered in practice, but its leukemic variant, Sezary syndrome is somehow yet to be reported from India.

The majority of these patients are managed by hemato-oncologists rather than dermatologists since the options are mostly chemotherapy and rarely, allogeneic stem cell transplantation. Patient age, presence of lymph node disease, and peripheral blood involvement are the most essential poor prognostic markers in advanced stages, especially those with erythroderma or tumor development in the background of erythroderma.\(^\text{(2,4,22,24)}\)

Many centers across the world prefer immunobiologic therapy, but extracorporeal photopheresis is not available. Newer targeted biologics such as alemtuzumab or mogamulizumab have also not been available.\(^\text{(34,35)}\)

Single-agent chemotherapy regimens, such as liposomal doxorubicin and gemcitabine, are offered at our centers. The responses are short lived but can provide clinical relief. Single-agent low-dose oral MTX and chlorambucil are other palliative options, the former being drug most Indian dermatologists are well versed with using. Although TSEB is not very effective in erythrodermic MF, it can be used with palliative intent.

Although systemic multiagent chemotherapy is opted in advanced disease, studies demonstrate no survival benefit over “conservative” sequential therapy.\(^\text{(36)}\) However, after multiagent chemotherapy, these patients can be treated with skin-directed therapies since they are mostly left with cutaneous patches and plaques.

The choice thus depends on patient factors, the disease aggressiveness, and the risks of myelosuppression with the drugs being used. Drugs include alkylating agents (cyclophosphamide and chlorambucil), anthracyclines, etoposide, and purine analogs. There is no multiagent chemotherapy regimen that has been found superior though cyclophosphamide, doxorubicin, vincristine, and prednisolone has been traditionally used.
Allogeneic transplantation in patients with advanced-stage MF can be considered as consolidation once complete or partial remission is achieved with discussed options.[37]

**Conclusion**

Patients need to have a confirmed diagnosis, workup for therapy, and prognostication. MF is an indolent disease in its early stages, but 25% can progress. Hence, if there is any suspicion of transformation, resistance to therapy, or intermediate or high risk, these patients should be referred to appropriate centers with multidisciplinary teams comprising dermatologists, hemato-oncologists, radiotherapists, and allied specialists to manage. The choice of therapy should finally depend on variables as discussed with minimal toxicities, even if they result in partial remission. Further studies into biology and availability of newer and targeted drugs will enable physicians in India to treat their patients with MF better.

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**Conflicts of interest**

There are no conflicts of interest.

**What is new?**

- Risk based approach practical over TNMB alone.
- Therapeutic options including TSEB are vital for patients in India who have limited access to newer drugs.
- Need for a national registry for epidemiological data for MF.

**References**

1. Pimpinelli N, Olsen EA, Santucci M, Vonderheid E, Haeffner AC, Stevens S, et al. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-63.
2. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: A population-based study of 3884 cases. Blood 2009;113:5064-73.
3. Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH. Review of the treatment of mycosis fungoides and sézary syndrome: A stage-based approach. J Natl Compr Canc Netw 2008;6:436-42.
4. Trautinger F, Knobler R, Willemze R, Peris K, Stadler R, Laroche L, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. Eur J Cancer 2006;42:1014-30.
5. Dummer R, Dreiling M; ESMO Guidelines Working Group. Primary cutaneous lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:i72-6.
6. Sugaya M, Hamada T, Kawai K, Yonekura K, Ohtsuka M, Shimauchi T, et al. Guidelines for the management of cutaneous lymphomas (2011): A consensus statement by the Japanese Skin Cancer Society – Lymphoma Study Group. J Dermatol 2013;40:2-14.
7. Doshi BR, Khopkar US. Retrospective study of spectrum of cutaneous lymphoma presenting to dermatology. Indian J Dermatol Venereol Leprol 2011;77:512-5.
8. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:173-22.
9. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: Clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139:857-66.
10. van Doorn R, Van Haselen CW, van Voorst Vader PC, Geerts ML, Heule F, de Rie M, et al. Mycosis fungoides: Disease evolution and prognosis of 309 Dutch patients. Arch Dermatol 2000;136:504-10.
11. Scarisbrick JJ, Kim YH, Whittaker SJ, Wood GS, Vermeer MH, Prince HM, et al. Prognostic factors, prognostic indices and staging in mycosis fungoides and Sézary syndrome: Where are we now? Br J Dermatol 2014;170:1226-36.
12. Arulogun SO, Prince HM, Ng J, Lade S, Ryan GF, Blevitt O, et al. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood 2008;112:3082-7.
13. Willemze R. Prognostic factors in cutaneous T cell lymphoma. Hematol Meet Rep 2009;3:123-30.
14. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, et al. Cutaneous lymphoma international consortium study of outcome in advanced stages of mycosis fungoides and Sézary syndrome: Effect of specific prognostic markers on survival and development of a prognostic model. J Clin Oncol 2015;33:3766-73.
15. Benton EC, Crichton S, Talpur R, Agar NS, Fields PA, Wedgeworth E, et al. A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome. Eur J Cancer 2013;49:2859-68.
16. Diamandidou E, Colome-Grimmer M, Fayad L, Duvic M, Kurzrock R. Transformation of mycosis fungoides/Sézary syndrome: Clinical characteristics and prognosis. Blood 1998;92:1150-9.
17. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011;29:2598-607.
18. Pope E, Weitzman S, Nga B, Walsh S, Morel K, Williams J, et al. Mycosis fungoides in the pediatric population: Report from an international Childhood Registry of Cutaneous Lymphomas. J Cutan Med Surg 2010;14:1-6.
19. Dogra S, Mahajan R. Phototherapy for mycosis fungoides. Indian J Dermatol Venereol Leprol 2015;81:124-35.
20. van Geel N, Speeckaert M, Chevolet I, De Schepper S, Lapeere H, de Rie M, et al. The treatment of mycosis fungoides and Sézary syndrome: Clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139:857-66.
21. Thomas TO, Agrawal P, Guitart J, Rosen ST, Rademaker AW, Quefeld C, et al. Outcome of patients treated with a single-fraction dose of palliative radiation for cutaneous T-cell lymphoma. Int J Radiat Oncol Biol Phys 2013;85:747-53.
22. Whittaker S, Hoppe R, Prince HM. How I treat mycosis fungoides and Sézary syndrome. Blood 2016;127:3142-53.
23. Berthelot C, Rivera A, Duvic M. Skin directed therapy for mycosis fungoides: A review. J Drugs Dermatol 2008;7:655-66.
24. Humme D, Nast A, Erdmann R, Vandersee S, Beyer M.
Systematic review of combination therapies for mycosis fungoides. Cancer Treat Rev 2014;40:927-33.

25. Lindelöf B, Sigurgeirsson B, Tegner E, Larkö O, Johannesson A, Berne B, et al. PUVA and cancer risk: The Swedish follow-up study. Br J Dermatol 1999;141:108-12.

26. Carter J, Zug KA. Phototherapy for cutaneous T-cell lymphoma: Online survey and literature review. J Am Acad Dermatol 2009;60:39-50.

27. Nikolaou V, Siakantaris MP, Vassilakopoulos TP, Papadavid E, Stratigos A, Economidi A, et al. PUVA plus interferon α2b in the treatment of advanced or refractory to PUVA early stage mycosis fungoides: A case series. J Eur Acad Dermatol Venereol 2011;25:354-7.

28. Whittaker S, Ortiz P, Dummer R, Ranki A, Hasan B, Meulemans B, et al. Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: Final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056). Br J Dermatol 2012;167:678-87.

29. Cheeley J, Sahn RE, DeLong LK, Parker SR. Acitretin for the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 2013;68:247-54.

30. Knobler RM, Trautinger F, Radaszkiewicz T, Kokoschka EM, Micksche M. Treatment of cutaneous T cell lymphoma with a combination of low-dose interferon alfa-2b and retinoids. J Am Acad Dermatol 1991;24 (2 Pt 1):247-52.

31. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: A retrospective study in 69 patients. J Am Acad Dermatol 2003;49:873-8.

32. Avilès A, Nambo MJ, Neri N, Castañeda C, Cleto S, Gonzalez M, et al. Interferon and low dose methotrexate improve outcome in refractory mycosis fungoides/Sézary syndrome. Cancer Biother Radiopharm 2007;22:836-40.

33. Hoppe RT, Harrison C, Tavallae M, Bashey S, Sundram U, Li S, et al. Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: Results of a pooled analysis from 3 phase-II clinical trials. J Am Acad Dermatol 2015;72:276-92.

34. de Masson A, Guitera P, Brice P, Moulounguet I, Mouly F, Bouaziz JD, et al. Long-term efficacy and safety of alemtuzumab in advanced primary cutaneous T-cell lymphomas. Br J Dermatol 2014;170:720-4.

35. Duvic M, Evans M, Wang C. Mogamulizumab for the treatment of cutaneous T- cell lymphoma: Recent advances and clinical potential. Ther Adv Hematol 2016;7:171-4.

36. Hughes CF, Khot A, McCormack C, Lade S, Westerman DA, Twigger R, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sézary syndrome: A comparative study of systemic therapy. Blood 2015;125:71-81.

37. Burt RK, Guitart J, Traynor A, Link C, Rosen S, Pandolfino T, et al. Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides: Evidence of a graft-versus-tumor effect. Bone Marrow Transplant 2000;25:111-3.