National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 2.2015

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Mycosis Fungoides/ Sezary Syndrome

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Mycosis Fungoides/Sezary Syndrome

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Discussion

DIAGNOSIS

ESSENTIAL:

- **Biopsy of suspicious skin sites**
- **Dermatopathology review of slides**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **IHC panel of skin biopsy[a,b,c]**
  - **CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, βF1, TCR-CγM1**
- **Molecular analysis of skin biopsy: TCR gene rearrangements (assessment of clonality)[a] by PCR methods[d]**
- **Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including:**
  - **Sezary cell prep**
  - **Flow cytometry (CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26) and**
  - **PCR for TCR gene rearrangement**
- **Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)**
- **Assessment of HTLV-1[e] serology in at-risk populations. HTLV-1 PCR if serology is indeterminate**

→

WORKUP

ESSENTIAL:

- **Complete physical examination:**
  - **Examination of entire skin: assessment of %BSA (palm plus digits ≈1% BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)**
  - **Palpation of peripheral lymph node regions**
  - **Palpation for organomegaly/masses**
- **Laboratory studies:[f]**
  - **CBC with Sezary screen (manual slide review, "Sezary cell prep")**
  - **Sezary flow cytometric study (optional for T1);**
  - **TCR gene rearrangement of peripheral blood lymphocytes if blood involvement suspected**
  - **Comprehensive metabolic panel**
  - **LDH**
- **Imaging studies:**
  - **Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT (≥T2 or large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)**
- **Pregnancy testing in women of child-bearing age[g]**

USEFUL IN SELECTED CASES:

- **Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)**
- **Biopsy of suspicious lymph nodes for identical clones (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites**
- **Rebiopsy if suspicious of large cell transformation**
- **Neck CT**

STAGE
(MFSS-2 and MFSS-3)

- **Stage IA** → **See Primary Treatment (MFSS-4)**
- **Stage IB-IIA** → **See Primary Treatment (MFSS-5)**
- **Stage IIB** → **See Primary Treatment (MFSS-6)**
- **Stage III** → **See Primary Treatment (MFSS-7)**
- **Stage IV** → **See Primary Treatment (MFSS-8)**

[a] Clinically or histologically non-diagnostic cases. Pimpinelli N, Olsen EA, Santucci M, et al, for the International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063.

[b] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[c] Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.

[d] TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.

[e] See map for prevalence of HTLV-1 by geographic region.

[f] Sezary syndrome (B2) is as defined on MFSS-2.

[g] Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TNMB		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome[h,i]
Skin	T1	Limited patches,[j] papules, and/or plaques[k] covering <10% of the skin surface
	T2	Patches,[j] papules, and/or plaques[k] covering ≥10% of the skin surface
	T2a	Patch only
	T2b	Plaque ± patch
	T3	One or more tumors[l] (≥1 cm in diameter)
	T4	Confluence of erythema ≥80% body surface area
Node	N0	No abnormal lymph nodes; biopsy not required
	N1	Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Abnormal lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
	MX	Abnormal visceral site; no histologic confirmation
Blood	B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells
	B1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sezary) cells but do not meet the criteria of B2
	B2	High blood tumor burden: ≥1000/mcL Sezary cells[i] or CD4/CD8 ≥10 or ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells

[h] Adapted from Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

[i] Sezary syndrome (B2) is defined as a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin) and either ≥1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of ≥10 or increase in CD4 cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD4+/CD26- of the total lymphocyte count).

[j] Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

[k] Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large cell transformation (≥25% large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

[l] Tumor = at least one >1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

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Clinical Staging of MF and SS[h]

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1–2	1,2	0	0,1
IIB	3	0–2	0	0,1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

[h]Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

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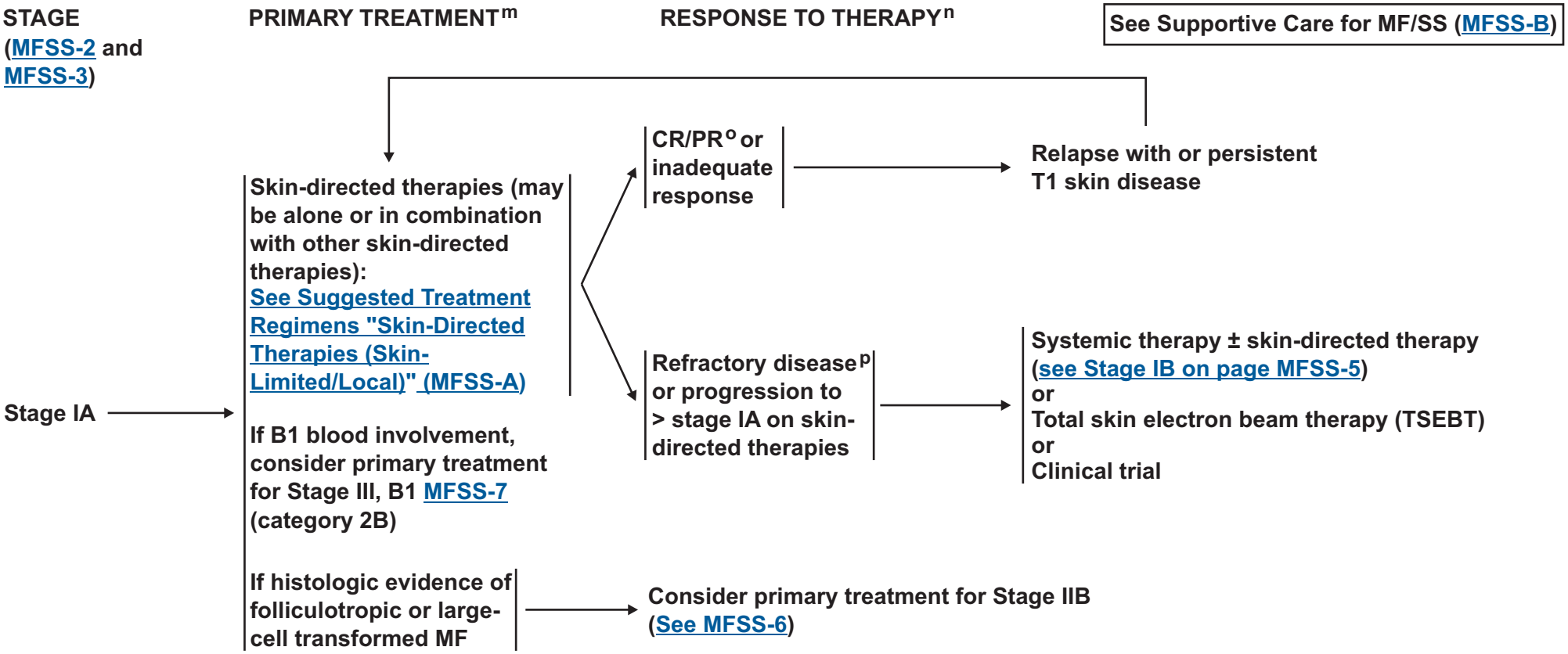
Mycosis Fungoides/Sezary Syndrome



[m] It is preferred that treatment occur at centers with expertise in the management of the disease.

[n] Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

[o] Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p] Refractory or intolerant to multiple previous therapies.

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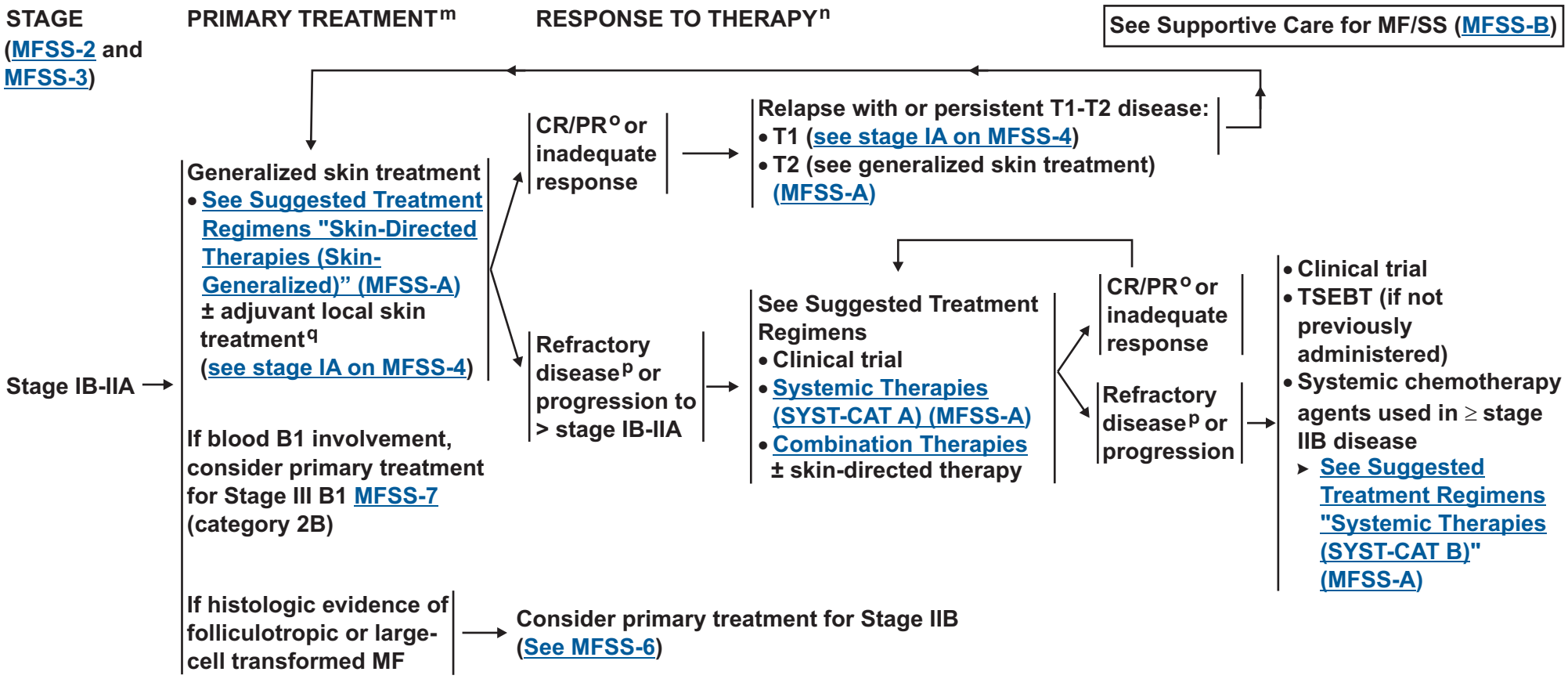

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[p] Refractory or intolerant to multiple previous therapies.

[q] For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.

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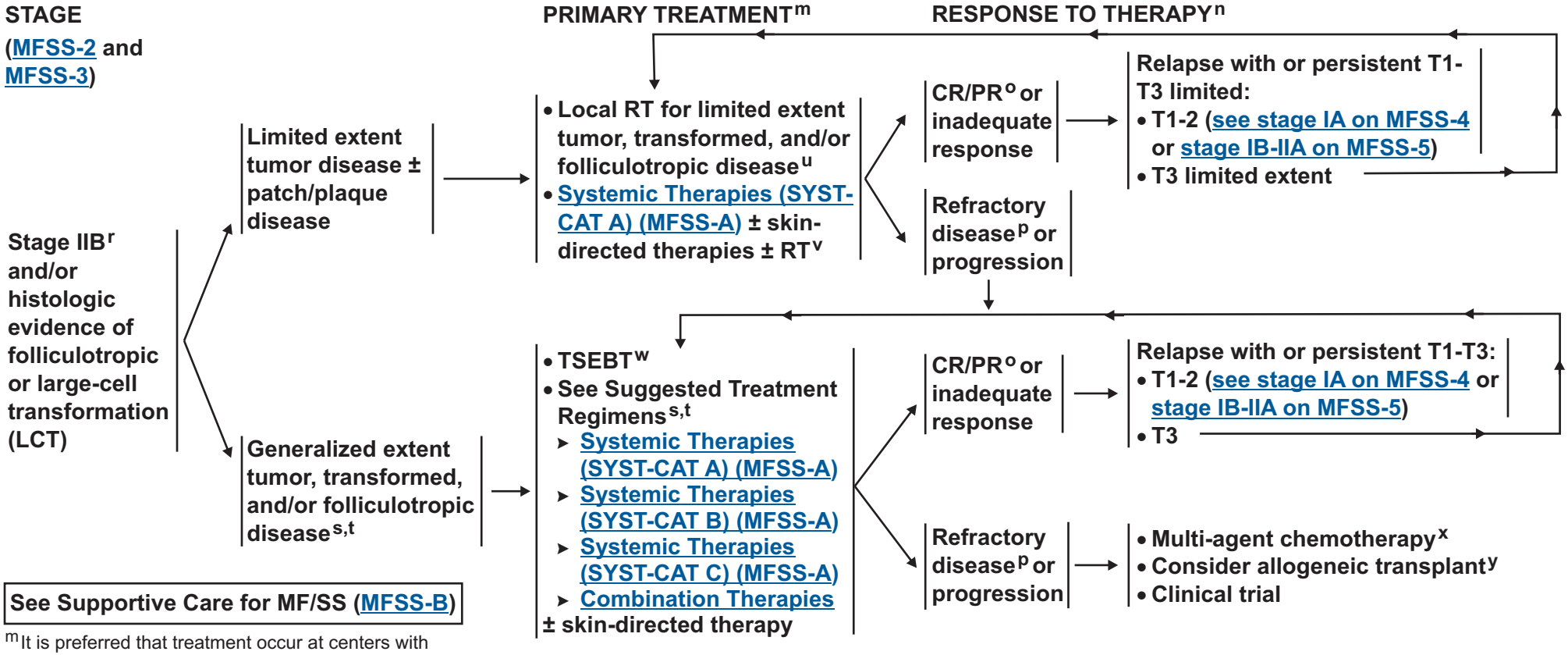

See Supportive Care for MF/SS (MFSS-B)

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[p] Refractory or intolerant to multiple previous therapies.

[r] Rebiopsy if suspect large cell transformation.

[s] Histologic evidence of LCT often, but not always corresponds to a more aggressive growth rate. If there is no evidence of more aggressive growth, choosing systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[t] Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before resorting to treatments listed in SYST CAT B or SYST CAT C.

[u] For non-radiated sites, see Stage I-IIA. After patient is rendered disease free by RT, may consider adjuvant systemic biologic therapy (SYST-CAT A) after RT to improve response duration.

[v] RT is preferred for tumor lesions.

[w] May consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration.

[x] Most patients are treated with multiple SYST-CAT A/B or combination therapies before receiving multiagent chemotherapy.

[y] The role of allogeneic HSCT is controversial. See Discussion for further details.

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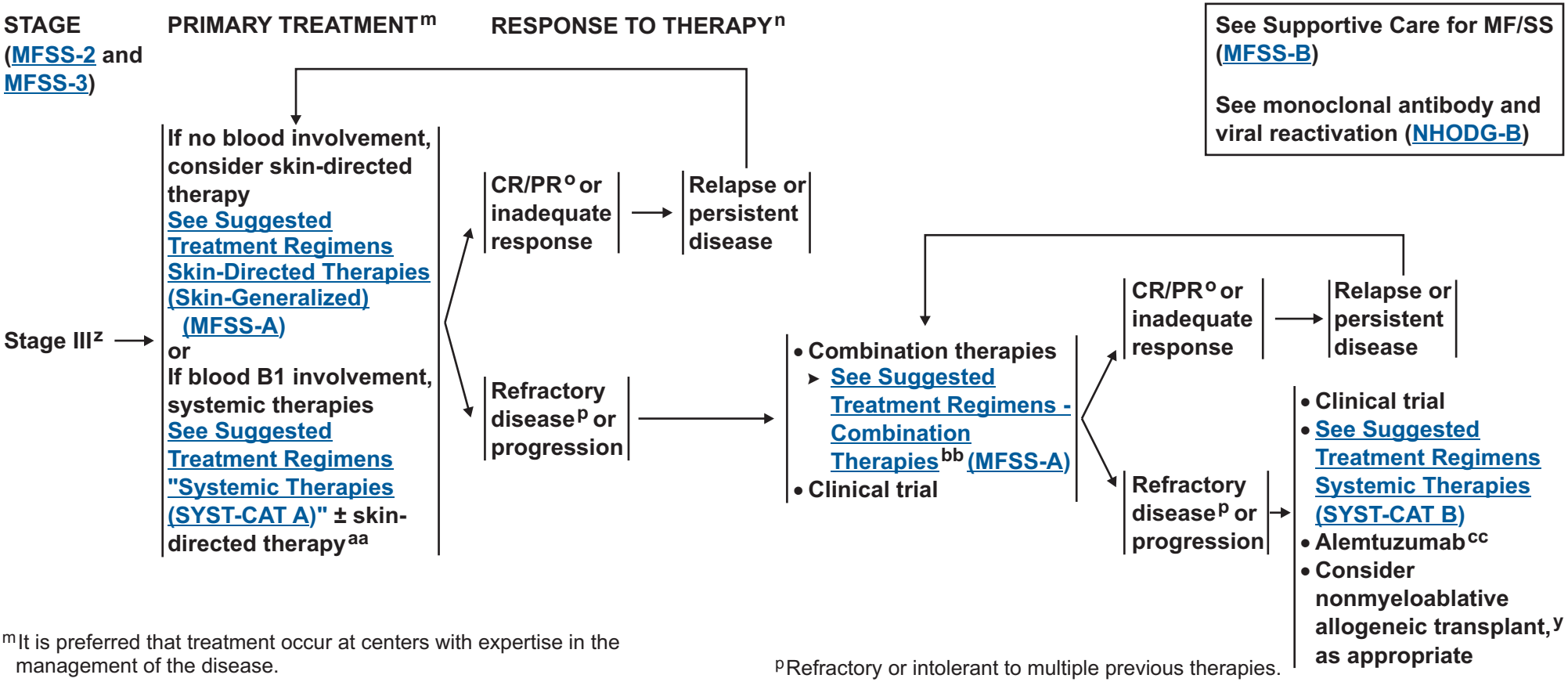

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[o] Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p] Refractory or intolerant to multiple previous therapies.

[y] The role of allogeneic HSCT is controversial. See Discussion for further details.

[z] Generalized skin-directed therapies (other than topical steroids) may not be well-tolerated in stage III and should be used with caution. Phototherapy (PUVA or UVB) or TSEBT can be used successfully.

[aa] Mid-potency topical steroids should be included (± occlusive modality) with any of the primary treatment modalities to reduce skin symptoms. Erythrodermic patients are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered.

[bb] Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.

[cc] Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

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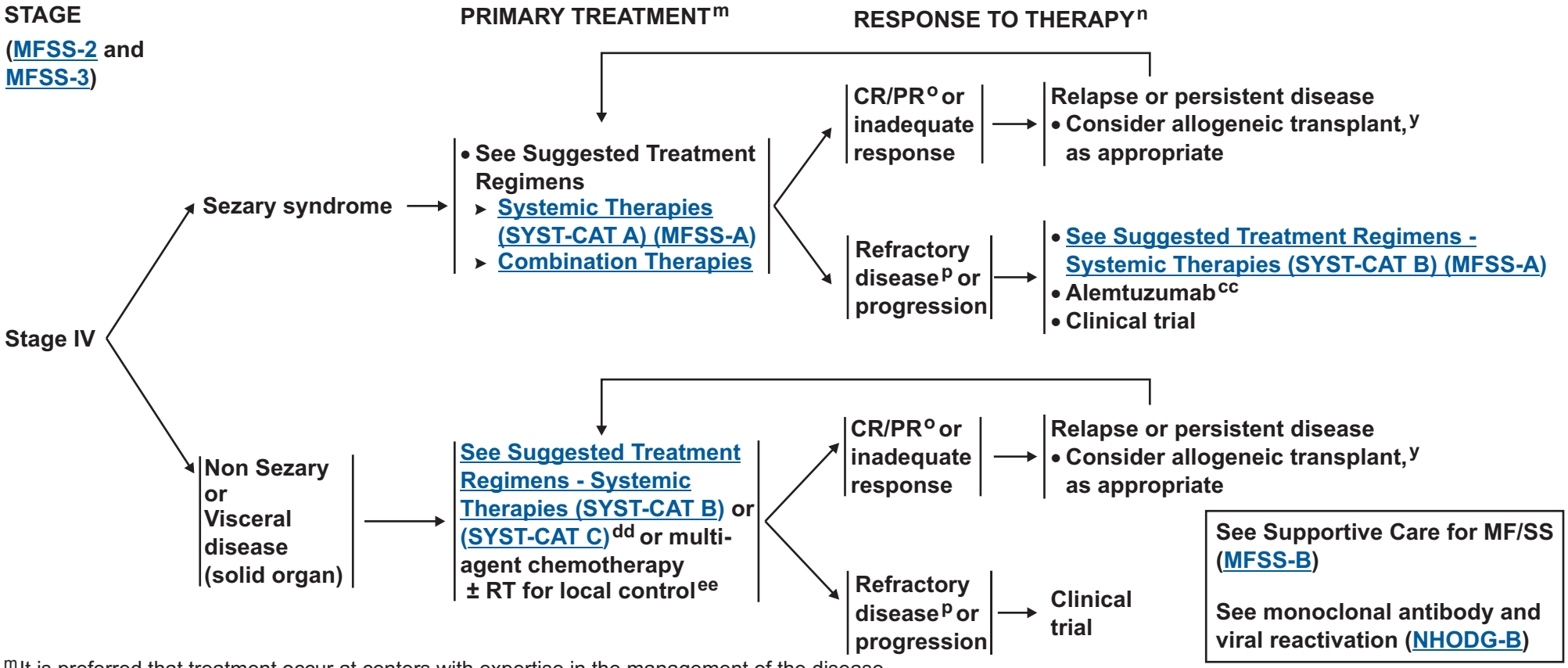

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[p] Refractory or intolerant to multiple previous therapies.

[y] The role of allogeneic HSCT is controversial. See Discussion for further details.

[cc] Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

[dd] Patients with stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[ee] Consider adjuvant systemic biologic therapy (SYST-CAT A) after chemotherapy to improve response duration.

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SUGGESTED TREATMENT REGIMENS[a]

SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Local radiation (8–36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)[c]
- Topical imiquimod

For generalized skin involvement (Skin-Generalized)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Phototherapy (UVB, NB-UVB, for patch/thin plaques; PUVA for thicker plaques)[c]
- Total skin electron beam therapy (TSEBT) (12-36 Gy)[d] (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies)

SYSTEMIC THERAPIES

Category A (SYST-CAT A)
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)[e]
- Extracorporeal photopheresis[f]
- Methotrexate (≤100 mg q week)

Category B (SYST-CAT B)
- First-line therapies (alphabetical order)
  - Brentuximab vedotin
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)[g] (alphabetical order)
- Brentuximab vedotin
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B[h]

COMBINATION THERAPIES

Skin-directed + Systemic
- Phototherapy + retinoid[e]
- Phototherapy + IFN
- Phototherapy + photopheresis[f]
- Total skin electron beam + photopheresis[f]

Systemic + Systemic
- Retinoid + IFN
- Photopheresis[f] + retinoid
- Photopheresis[f] + IFN
- Photopheresis[f] + retinoid + IFN

[a] See references for regimens MFSS-A 2 of 4, MFSS-A 3 of 4, and MFSS-A 4 of 4.

[b] Long-term use of topical steroid may be associated with skin atrophy and/or striae formation. This risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption.

[c] Cumulative dose of UV is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy may not be appropriate in patients with a history of extensive squamoproliferative skin neoplasms or basal cell carcinomas or who have had melanoma.

[d] It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response.

[e] Safety of combining TSEBT with systemic retinoids or HDAC inhibitors, such as vorinostat or romidepsin, or combining phototherapy with vorinostat or romidepsin is unknown.

[f] Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

[g] Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.

[h] Combination regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease.

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SUGGESTED TREATMENT REGIMENS
References

Skin-directed Therapies

Topical corticosteroids

Zackheim HS, Kashani Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol 1998;134(8):949-954.

Zackheim HS. Treatment of patch stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283-287.

Nitrogen mustard (mechlorethamine hydrochloride)

Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: Update of the Stanford experience. Arch Dermatol 2003;139:165-173.

Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol 2013;149:25-32.

Local radiation

Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides). Int J Radiat Oncol Biol Phys 1998;40:109-115.

Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154-158.

Thomas TO, Agrawal P, Guitart J, 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;85:747-753

Topical bexarotene

Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin directed treatment of patients with cutaneous T cell lymphoma. Arch Dermatol 2002;138:325-332.

Heald P, Mehlmauer M, Martin AG, et al. Topical bexarotene therapy for patients with refractory or persistent early stage cutaneous T cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003;49:801-815.

Tazarotene Gel

Apisarnthanarax N, Talpur R, Ward S, Ni X, Kim HW, Duvic M. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol 2004;50:600-607.

Topical imiquimod

Deeths MJ, Chapman JT, Dellavalle RP, Zeng C, Aeling JL. Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. J Am Acad Dermatol 2005;52:275-280.

Phototherapy (UVB and PUVA)

Gathers RC, Scherschun L, Malick F, Fivenson DP, Lim HW. Narrowband UVB phototherapy for early stage mycosis fungoides. J Am Acad Dermatol 2002;47:191-197.

Querfeld C, Rosen ST, Kuzel TM, et al. Long term follow up of patients with early stage cutaneous T cell lymphoma who achieved complete remission with psoralen plus UVA monotherapy. Arch Dermatol 2005;141:305-311.

Ponte P, Serrao V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. J Eur Acad Dermatol Venereol 2010;24:716-721.

Total skin electron beam therapy (TSEBT)

Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. Int J Radiat Oncol Biol Phys 1999;43:951-958.

Ysebaert L, Truc G, Dalac S et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides. Int J Radiat Oncol Biol Phys 2004;58:1128-1134.

Harrison C, Young J, Navi D, et al. Revisiting low-dose total skin electron beam therapy in mycosis fungoides. Int J Radiat Oncol Biol Phys 2011;81:e651-657.

Systemic Therapies

Alemtuzumab for Sezary syndrome ± lymph node disease

Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003;101:4267-4272.

Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007;92:784-794.

Gautschi O, Blumenthal N, Streit M, et al. Successful treatment of chemotherapy-refractory Sezary syndrome with alemtuzumab (Campath-1H). Eur J Haematol 2004;72:61-63.

Querfeld C, Mehta N, Rosen ST, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. Leuk Lymphoma 2009;50:1969-1976.

Brentuximab vedotin

Tetzlaff M, Clos AL, Gangar P, Talpur R. Phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphomas and lymphoproliferative disorders [abstract]. Blood 2013;122:Abstract 367.

Kim Y, Tavallaee M, Rozati S, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides or Sezary syndrome: Final results show significant clinical activity and suggest correlation with CD30 expression [abstract]. Blood 2014;124:Abstract 804.

Retinoids

Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther 2006;19:264-271.

Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001;137:581-593.

Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001;19:2456-2471.

Interferon

Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003;16:311-321.

Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208-212.

Continued on next page

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SUGGESTED TREATMENT REGIMENS
References

Systemic Therapies Continued

Vorinostat
Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31-39.
Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109-3115.
Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416.

Romidepsin
Piekarz RL, Frye R, Turner M, et al. Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma. J Clin Oncol 2009;27:5410-5417.
Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010; 28:4485-4491.

Extracorporeal photopheresis (ECP)
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Note: All recommendations are category 2A unless otherwise indicated.
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SUGGESTED TREATMENT REGIMENS
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Combination Therapies

Skin-directed + Systemic

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SUPPORTIVE CARE FOR MF/SS

Pruritus

- Assessment
  - Pruritus should be assessed at each visit using consistent measurements
  - Generalized pruritus and localized pruritus should be distinguished
  - Correlation between sites of disease and localization of pruritus should be noted
  - Other potential causes for pruritus should be ruled out

- Treatment
  - Moisturizers, emollients, and barrier protection
  - Topical steroid (appropriate strength for body region) ± occlusion
  - Optimize skin-directed and systemic therapy
  - Topical preparations - camphor/menthol formulations, pramoxine formulations
  - Systemic agents
    - First-line
      - Antihistamines
      - Doxepin
      - Gabapentin
    - Second-line
      - Aprepitant
      - Mirtazapine
      - Selective serotonin reuptake inhibitors
    - Third-line
      - Naltrexone

Infections

- Active or Suspected Infections
  - Cutaneous viral infections
    - High risk for skin dissemination of localized viral infections (HSV/VZV)
  - Erythroderma:
    - Skin swab and nares cultures for Staphylococcus aureus (S. aureus) infection or colonization
    - Intranasal mupirocin
    - Oral dicloxacillin or cephalexin
    - Sulfamethoxazole/trimethoprim, doxycycline if suspect MRSA
    - Vancomycin if no improvement or bacteremia
    - Bleach baths or soaks (if limited area)
  - Ulcerated and necrotic tumors:
    - Gram-negative rods (GNR) common in necrotic tumors may lead to bacteremia and sepsis
    - If high suspicion for infection, obtain blood cultures, start antibiotics even if fever absent
    - Role of wound cultures not clear due to colonization
    - Empirical therapy for both GNR and gram-positive coccal infections is necessary initially
- Prophylaxis
  - Optimize skin barrier protection
  - Mupirocin for S. aureus colonization
  - Bleach baths or soaks (if limited area)
  - Avoid central lines (especially in erythrodermic patients)
  - For patients receiving alemtuzumab, see NHODG-B.

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Mycosis Fungoides and Sézary Syndrome

Cutaneous T-cell lymphomas (CTCLs) are a group of NHLs that primarily develop in the skin, and at times progress to involve lymph nodes, blood and visceral organs. In a recent population based study of 3884 cases of cutaneous lymphomas diagnosed during 2001-2005, CTCLs accounted for 71% of cases compared with 29% for cutaneous B-cell lymphomas.[1] Based on data from the SEER program registries for the period 1998 to 2002, the annual incidence rate of CTCL was 9.6 per 1 million persons.[2] Mycosis fungoides (MF) is the most common type of CTCLs. MF accounts for about 50% to 70% of CTCL cases while Sézary syndrome (SS) accounts for only 1% to 3% of cases.[1-3] MF is an extranodal NHL of mature T-cells with primary cutaneous involvement. SS is an erythrodermic, leukemic variant of CTCL and it is characterized by significant blood involvement and lymphadenopathy. In updated EORTC and WHO classification of CTCL, MF is characterized as an indolent neoplasm.[3]

Large cell transformation (LCT) has been documented in a subgroup of patients with MF and is diagnosed when large cells are present in more than 25% of lymphoid/tumor cell infiltrates in a skin lesion biopsy.[4,5] Expert hematopathology review is needed to confirm the diagnosis, as LCT may not be easily distinguishable from other lymphoproliferative disorders. The incidence of LCT is strongly dependent on the stage of the disease at diagnosis (1.4% in early-stage disease, compared with 27% for stage IIB disease and 56%-67% for stage IV disease).[6] In published reports, the median OS from time of diagnosis of LCT ranged between 19 and 36 months.[4-7] However, in a recent study based on a large cutaneous lymphoma database, the median OS was 8.3 years and the 5-year OS rate was 63% for patients with LCT (n=70).[8] Multivariate analysis from this study showed that LCT was significantly associated with risk of disease progression but not with OS outcomes. LCT is often, but not always, aggressive. CD30 expression of tumor cells is associated with LCT in MF or SS in 30-50% of cases.[4,6,7] This finding may have potential implications for CD30-directed therapies.

Prognosis

Published reports have identified the most significant prognostic factors for survival in patients with MF to include age at presentation, extent and type of skin involvement (T classification), overall stage, presence of extracutaneous disease and peripheral blood involvement.[8-12] Patients diagnosed with limited patch or plaque disease have an excellent prognosis, whereas those with tumor stage disease or erythrodermic skin involvement have a less favorable prognosis; patients with extracutaneous disease have a poor prognosis. Long-term follow-up data from a retrospective cohort study involving 525 patients with MF and SS showed that patient age, T classification, and presence of extracutaneous disease retained independent prognostic value in a multivariate analysis.[12] The risk of disease progression, development of extracutaneous disease or death due to MF was correlated with initial T classification. In a retrospective cohort study of 106 patients with erythrodermic MF and SS, older age, advanced disease and peripheral blood involvement were identified as adverse prognostic factors.[10] Three distinct prognostic groups (favorable, intermediate and unfavorable) were identified according to the number of unfavorable prognostic factors: 65 years or older at presentation, lymph node or visceral (stage IV) disease and peripheral blood involvement. The median survival by risk group was 10.2, 3.7, and 1.5 years, respectively.[10] In a retrospective analysis involving a large number of patients with CTCL (N=1197), the median OS in the group of patients with erythrodermic CTCL (n=124) was 5.1 years (range, 0.4–18.6 years).[13] The extent of blood involvement (as defined by flow cytometric measurements of Sézary cell counts) was significantly correlated with

survival outcomes. In multivariate analysis, advanced age and elevated lactate dehydrogenase (LDH) were the strongest predictors of poor OS.[13] In a study based on data from patients with MF/SS (N=1502) registered in a large cutaneous lymphoma database, multivariate analysis showed that advanced skin (T) stage, peripheral blood involvement, elevated LDH, and folliculotropic MF were independent factors predictive of increased risk of disease progression and decreased OS.[8] A recent study reported long-term outcomes in a large cohort of patients with MF/SS (N=1263) from a single center (seen between 1982–2009).[14] Most patients (71.5%) presented with early-stage MF (stage IA–IIA) at the time of diagnosis. Median progression-free survival (PFS) and OS was 16 years and 24 years, respectively. Approximately 12% of patients had disease progression to a higher stage, and 8% died due to the disease.[14] Significant independent factors associated with risks for progression or death included age, plaque stage, LDH levels, and tumor area.[14]

Diagnosis

In the algorithms developed by the ISCL, the diagnosis of MF is based on integration of clinical, histopathologic, immunopathologic, and molecular biological characteristics.[15] According to the revised criteria, significant blood involvement (B2) observed in SS is defined by the presence of T cells with a clonal T-cell receptor (TCR) gene rearrangement in the blood (clonally related to neoplastic T cells in the skin) and either an absolute Sézary cell count of 1000 cells/mcL or more, or increased CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or higher or increased CD4+ cells with an abnormal phenotype (≥ 40% CD4+/CD7- or ≥ 30% CD4+/CD26- of total lymphocytes).

Complete skin examination, biopsy of suspicious skin sites and immunohistochemical studies of skin biopsy are essential to confirm the diagnosis. Biopsy of suspicious lymph nodes and assessment of peripheral blood for Sézary cells are recommended in the absence of a definitive skin diagnosis. MF and SS cells are characterized by the following immunophenotype: CD2+, CD3+, CD5+, CD4+, CD8-, CCR4+, CD45RO+ and they lack certain T-cell markers, CD7 and CD26.[16] There are subtypes of MF that are also CD8+, although rare. If histological evidence of large cell transformation (LCT) is observed, phenotyping with CD30 is recommended. The T-cells also express cutaneous lymphocyte antigen (CLA) and TH2 cytokines. They are also associated with a loss of TH1 and IL-12 cytokines. TCR gene rearrangement should be interpreted with caution since TCR clonal rearrangements can also be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases. TCR gene rearrangement analysis by PCR is a useful technique to support the diagnosis of MF/SS and to distinguish MF from inflammatory dermatoses, especially if identical clones are demonstrated in more than one skin sites.[17] A recent study evaluated the sensitivity and specificity of PCR-based TCRG and TCRB clonality tests in distinguishing MF from inflammatory dermatoses, and reported that the combined use of these tests (in sequence) was more useful than a TCRG test alone; the researchers proposed an algorithm for the sequential use of these tests in patients with intermediate pretest probabilities of having MF.[18] In at-risk populations, assessment of HTLV-1 status may be useful. HTLV-1 serology can be assessed by ELISA, and if positive, a confirmed by western blot. If the result from western blot is indeterminate, then PCR analysis for HTLV-1 can be performed.

Staging

The TNM staging system developed by the Mycosis Fungoides Cooperative Group (MFCG) had been the standard for staging and classification of patients with MF and SS.[19] Recently, the International Society for Cutaneous Lymphomas (ISCL) and EORTC recommended revisions to the MFCG staging system based on new data that emerged in the area of immunohistochemistry, biology and prognosis of MF and SS following the MFCG publication.[20,21] In the revised staging system, all staged patients should have a definitive diagnosis of MF and SS. T1 disease is defined as less than 10% of the skin surface involvement with patches or plaques and T4 disease is defined as erythroderma with at least 80% of the skin surface diffusely involved. The extent of skin involvement is based on the percentage of body surface area (BSA) where the patient's palm (without digits) is equivalent to 0.5% BSA and the palm with all 5 digits is equivalent to 1% BSA. Lymph node biopsy for staging is recommended only for clinically abnormal nodes (>1.5 cm in diameter). However, the designation "Nx" may be used for abnormal lymph nodes without histologic confirmation. Visceral disease with the involvement of an organ (e.g., spleen, liver) other than the skin, nodes or blood should be documented using imaging studies. The designation "Mx" can be used for presence of abnormal visceral sites without histologic confirmation. Blood involvement is classified into three groups: B0 is associated with the absence of significant blood involvement (5% or less of Sézary cells); B1 is defined as having a low tumor burden (more than 5% of Sézary cells but does not meet the criteria for B2); B2 is associated with high tumor burden with more than 1000 Sézary cells/mcL or increase in CD4+ cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD+/CD26- of total lymphocytes). According to the updated staging system, patients with stage III are further divided into two subgroups, stages IIIA and IIIB, to differentiate based on the extent of blood involvement (B0 and B1, respectively).[20]

Workup

The initial workup of patients diagnosed with MF or SS involves a complete skin examination to assess the extent of the disease (i.e., percent of BSA), type of skin lesion (e.g., patch/plaque, tumor, erythroderma), and examination of lymph nodes or other masses for the evaluation of lymphadenopathy or organomegaly.[20] Laboratory studies should include CBC with Sézary screen (manual slide review to identify Sézary cells) and flow cytometry to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype. A comprehensive metabolic panel and assessment of LDH levels should also be part of the initial laboratory studies. Analysis of TCR gene arrangement of peripheral blood lymphocytes is recommended if blood involvement is suspected. Patients with unfavorable features (T2 or higher, folliculotropic MF or large cell transformation, palpable adenopathy or abnormal laboratory studies) should undergo either CT or PET-CT scan of the chest, abdomen and pelvis. A CT scan of the neck may be useful in some circumstances. Integrated PET-CT was found to be more sensitive for the detection of lymph node involvement than CT alone and can help direct biopsies.[22] Bone marrow biopsy is not required for disease staging, but may be helpful in those with suspected marrow involvement (include B2 blood involvement) or in those with an unexplained hematologic abnormality.[20] Biopsy of suspicious lymph nodes (i.e., palpable nodes >1.5 cm in diameter and/or firm, irregular, clustered or fixed nodes) is recommended with evaluation for TCR gene rearrangements,[20] especially due to the worse prognosis of patients with clonal rearrangement in lymph nodes.[23]

Treatment Options for MF and SS

Initial treatment in patients with patch/plaque disease consists of skin-directed therapies (localized or generalized), with the addition of milder systemic therapy ("SYST-CAT A"; see Guidelines page MFSS-A) for refractory, persistent, or progressive disease with skin-directed therapies. Those patients who have unfavorable prognostic features (e.g., folliculotropic or large-cell transformed MF, or B1 involvement) may have systemic therapies introduced earlier in the treatment algorithm. Patients who do not respond to biologic therapy or those with very aggressive or extracutaneous disease may be treated with chemotherapy.[24-26] Due to the rarity of the condition and the need for an individualized approach, referral to a multidisciplinary academic specialty center is preferred.

Skin-directed therapies

Localized skin-directed treatments include topical therapy with corticosteroids, mechlorethamine hydrochloride, carmustine, topical retinoids (e.g., bexarotene) or topical imiquimod, or local radiation therapy (RT). Generalized skin directed therapies such as phototherapy [UVB or PUVA (psoralen and UVA)] and total skin electronic beam therapy (TSEBT) are indicated in patients with widespread skin involvement (see Guidelines page MFSS-A under "Skin-directed therapies").

Topical corticosteroids are effective, especially for the treatment of patch-stage MF, producing response rates of over 90%.[27,28] However, long-term use of topical steroid may lead to skin atrophy or striae formation and the risk becomes greater with increased potency of the steroid. Moreover, high-potency steroid used on large skin surfaces may lead to systemic absorption. Topical chemotherapy with nitrogen mustard or carmustine has been used for the management of MF for many decades.[29,30] Long-term follow-up results from a retrospective cohort study in 203 patients with stage I-III MF have confirmed the activity and safety of topical therapy with this approach.[31] The overall response rate (ORR) was 83% (complete response [CR] in 50%). The 5-year relapse-free survival rate for patients with a CR was 42%. The median overall survival (OS) for the entire cohort was 16 years and the actuarial 10-year OS rate was 71%.[30] The efficacy with topical nitrogen mustard was similar for aqueous and ointment preparations, although the ointment was associated with reduced hypersensitivity reactions. Patients with T1 disease had higher ORR (93% vs. 72%) and CR rate (65% vs. 34%) than those with T2 disease. Moreover, patients with T1 disease had longer median OS (21 months vs. 15 months) and 5-year OS rate (97% vs. 72%) compared with patients with T2 disease.[30] A multicenter randomized phase II trial evaluated the efficacy of a topical gel formulation of the nitrogen mustard mechlorethamine compared with the compounded ointment formulation in patients with stage IA or IIA MF (N=260).[32] Eligible patients had not been treated with topical mechlorethamine within 2 years of study enrollment and had not received prior therapy with topical carmustine. Response rate based on Composite Assessment of Index Lesion Severity was 58.5% with the gel formulation compared with 48% for the ointment; these outcomes met non-inferiority criteria for the gel formulation arm. No study treatment-related serious adverse events were reported, and no systemic absorption was detected.[32]

Synthetic retinoids (bexarotene and tazarotene) and imiquimod have been used as topical therapy for the treatment of patients with MF and SS. FDA-approved bexarotene gel was evaluated in two open-label, historically-controlled clinical studies involving 117 patients with CTCL.[33,34] In the phase I-II trial involving 67 patients with early stage MF, the ORR was 63% (CR in 21%); the estimated median response

duration was 99 weeks.[33] Response rates were higher among the patients who had no prior therapy compared with those who had received prior topical therapies (75% vs. 67%). In the phase III multicenter study of 50 patients with early stage refractory MF, the ORR was 44% (CR in 8%).[34] In a small open-label pilot study in patients (N=20) with early patch or plaque MF lesions (stable or refractory to therapy), tazarotene 0.1% topical gel was reported to be a well-tolerated and active adjuvant therapy by clinical and histologic assessments.[35] In a small number of case studies, imiquimod was active in patients with early stage MF refractory to other therapies.[36-38] Bexarotene gel is the only FDA approved synthetic retinoid for topical therapy in patients with MF and SS. Given the common skin irritation toxicity observed with topical retinoids and imiquimod, these agents are best for treatment of localized, limited areas.

MF is extremely radiosensitive and patients with minimal stage IA MF may be managed effectively with local superficial RT without adjuvant therapy.[39] High disease-free survival (DFS) rates (75% at 5 years; 64% at 10 years) have been reported for patients with early stage disease treated with RT alone (N=21).[40] The 10-year DFS rate was 85% for patients with unilesional disease. The optimal RT dose was at least 20 Gy, which resulted in a DFS rate of 91% with no distant failures. In another report in patients with unilesional MF (n=18), treatment with local RT (most patients received RT dose of 30.6 Gy) resulted in an ORR of 100%, with a 10-year relapse-free survival (RFS) and OS rates of 86% and 100%, respectively.[41] TSEBT has been shown to be effective in patients with early stage MF, without the need for adjuvant therapy.[42] In patients with T1 or T2 disease (N=57) treated with TSEBT (mean total RT dose of 30 Gy), the ORR was 95%; CR was observed in 87.5% and 85% of patients with T1 and T2 disease, respectively.[42] After a median follow up of 114 months, the 5-year DFS and OS rates were 50% and 90%, respectively. The 10-year OS rate was 65%.[42] TSEBT has also been shown to be active in patients with thick generalized plaque (T2) or tumorous disease (T3). In a retrospective analysis involving 148 patients with T2 and T3 disease, TSEBT alone or in combination with adjuvant topical mechlorethamine hydrochloride yielded significantly higher CR rates compared with mechlorethamine hydrochloride alone (76% vs. 39% for T2; 44% vs. 8% for T3).[43] The standard dose of TSEBT is 30-36 Gy (given in fractions over 8 to 10 weeks), but recent studies suggest that lower radiation doses may be sufficiently active. A recent retrospective study in patients with T2 to T4 disease (N=102; excluded patients with extracutaneous disease) treated with TSEBT doses of 5 to <30 Gy showed ORR (>50% improvement) of 96% and CR rate of 31%.[44] The ORR among the subgroup that received 5 to <10 Gy (n=19), 10 to <20 Gy (n=52), and 20 to <30 Gy (n=32), were 90%, 98% and 97%, respectively. The CR rate with TSEBT 5 to <30 Gy was higher among patients with T2 compared with T3 disease (41% vs. 17%).[44] In patients with T2 or T3 disease, OS and PFS outcomes were not significantly different by dose groups and were comparable to that of standard dose TSEBT (i.e., ≥30 Gy).[44] The lower dose ranges with TSEBT 10 to <20 Gy warrants further evaluation, especially in combination regimens. In a recent prospective study, patients with stage IB-IV MF (N=10) were treated with TSEBT 1 Gy weekly (for a total dose of 10 Gy).[45] The ORR was 90% and 70% achieved a CR or very good partial remission (PR)(<1% skin affected by patches/plaques). The median duration of response was 5 months. Low dose of TSEBT was well tolerated in this patient population; further studies of its use in combined modality regimens are warranted.

Phototherapy with UVB (including narrowband) and photochemotherapy with psoralen and UVA (PUVA) are effective alternative treatment options for patients with early stage MF.[46-49] In a retrospective analysis

of patients with stage IA or IB (N=56), phototherapy with narrowband UVB (n=21) and PUVA (n=35) produced similar CR rates (81% vs. 71%) and mean relapse-free interval (24.5 months vs. 23 months).[46] In another retrospective study in a larger group of patients with early-stage MF (stages IA–IIA; N=114), treatment with narrowband UVB (n=19) and PUVA (n=95) also resulted in similar CR rates (68% vs. 62%) and median time to relapse (11.5 months vs.14 months).[48] In a retrospective analysis of long-term follow-up data from patients with early-stage MF (stages IA–IIA) who achieved a CR with PUVA (N=66), 10-year DFS rates were 30% for patients with stage IA disease and 50% for those with stage IB/IIA disease.[47] The median follow-up time was 94 months. The 10-year OS rates were 82% and 69%, respectively; interestingly, OS outcomes were not different by relapse status. A third of patients developed signs of chronic photodamage and secondary cutaneous malignancies.[47] It should be noted that cumulative doses of UV are associated with increased risk of UV-associated skin malignancies. Thus, phototherapy may not be appropriate for patients with a history of squamous or basal cell carcinoma or melanoma. Since narrowband UVB has less skin toxicity than broadband and PUVA, it is preferred to start with narrowband UVB than PUVA in early-stage patients with patch or thin plaque disease.

Systemic therapies

There are extensive data—although primarily from small clinical studies—on many systemic therapeutic options for CTCL. Historically, the response criteria for CTCL were poorly defined and validated response assessments were lacking. More recent studies have incorporated consensus response assessments and newer FDA-approved agents have undergone central review for efficacy outcomes.

Systemic therapies with extracorporeal photopheresis (ECP), interferons, systemic retinoids, or histone deacetylase (HDAC) inhibitors are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed therapies (see Guidelines page MFSS-A under "SYST-CAT A"). Multiagent chemotherapy is generally reserved only for patients who do not respond to multiple prior therapies (including single-agent chemotherapy and combination regimens) or those with bulky lymph node or solid organ disease. In the absence of other unfavorable prognostic features, it is recommended that systemic therapy be deferred until the patient has failed multiple treatments with local and skin-directed therapy.

ECP is an immunomodulatory therapy using psoralen and UVA extracorporeally. This approach involves the removal of leukocytes by leukapheresis, which are then treated with 8-methoxypsoralen, exposed to UVA and returned to the patient. ECP is a long standing treatment for MF, and is particularly indicated in patients with or at risk of blood involvement (erythrodermic stage III disease or IVA with SS).[50-52] In small retrospective studies with ECP (generally given for at least 6 months) in patients with CTCL, ORR ranged from about 50-70% with a CR in 15-25%; median OS was 6-8 years, and 5-year OS rate was reported to be 80% in one study.[52-54] In a meta-analysis of 19 studies (5 studies using ECP as monotherapy and 14 studies as combination therapy) involving more than 400 patients with CTCL, the combined ORR for all stages of CTCL was 56% with 18% achieving a CR.[51] ECP as monotherapy resulted in 55.5% ORR with 15% CR.[51] The corresponding response rates were 58% (15% CR) for erythrodermic disease (T4) and 43% (9.5% CR) for SS. Studies evaluating combination regimens with ECP are discussed below, in the section "Combination Therapies".

Retinoids [all-trans retinoic acid (ATRA),13-cis retinoic acid and their synthetic analogs acitretin and isotretinoin] and interferons have been used for many years for the treatment of CTCL.[55,56] Interferon (IFN)

alpha as a single agent has produced ORR greater than 70% with CR rates greater than 20%.[55] IFN gamma has been shown to be effective in the treatment of patients with various stages of CTCL that is refractory to IFN alpha and other topical or systemic therapies.[57]

Oral bexarotene has been evaluated for the treatment of refractory or persistent early- and advanced-stage CTCL in two multicenter clinical trials.[58,59] In patients with early-stage CTCL (stages IA-IIA) refractory to prior treatment, bexarotene was well tolerated and induced an ORR of 54% among patients treated at doses of 300 mg/m^2/day (n=28).[59] The rate of disease progression at this dose was 21%, and the median duration of response had not been reached at the time of the report. In patients with advanced CTCL (stages IIB–IVB) refractory to prior treatments, clinical CR and PR were observed in 45% of patients receiving 300 mg/m^2/day (n=56). At doses greater than 300 mg/m^2/day (n=38), the ORR was 55%, including 13% clinical CR.[58] Side effects were reversible and manageable with appropriate medications prior to initiation of treatment. In a retrospective comparison study, ATRA and bexarotene were reported to induce similar outcomes with modest single-agent activity in the treatment of patients with relapsed MF and SS.[60] Bexarotene (oral capsules) is approved by the FDA for the treatment of refractory CTCL.

HDAC inhibitors are a new class of drugs that are potent inducers of histone acetylation, cell cycle arrest and apoptosis. The activity and safety of the HDAC inhibitors vorinostat and romidepsin were evaluated in patients with refractory CTCL in phase II trials.[61-64] In a phase IIb study involving 74 patients (median 3 prior therapies) with persistent, progressive or refractory stage IB to IVA MF/SS, vorinostat resulted in an ORR of 30% and median time to progression of 5 months.[62] Median time to progression was greater than 9.8 months in responders with advanced disease (stage IIB or higher).[62] The response rates and median response durations appeared to be comparable to those obtained with bexarotene capsules and denileukin diftitox. Vorinostat was the first HDAC inhibitor to receive FDA approval for the treatment of patients with progressive, persistent, or recurrent CTCL, on or following two systemic therapies. A *post-hoc* subset analysis of patients who experienced clinical benefit with vorinostat in the previous phase IIb study and received 2 or more years of vorinostat therapy (n=6) provided some evidence for the long-term safety and clinical benefit of vorinostat in heavily pretreated patients, regardless of previous treatment failures.[65]

Romidepsin demonstrated single-agent activity in 2 open-label clinical studies [pivotal phase 2B study (GPI-04–0001) and NCI 1312 (supportive study)] of 167 patients with CTCL refractory to prior therapies.[64,66] The pivotal phase IIb study (GPI-04-0001) enrolled 96 patients with stage IB to IVA CTCL (71% had advanced stage disease ≥ stage IIB; median 2 prior systemic therapies).[64] The ORR was 34% (CR in 6%). Among patients with advanced stages of disease, 38% achieved an objective response (CR in 7%).[64,67] The median time to response was 2 months and the median duration of response was 15 months. Improvement in pruritus was observed in 28 of 65 patients (43%) with moderate to severe symptoms at baseline, including in 11 patients who did not achieve an objective response.[67] These results are consistent with the findings of the phase NCI 1312 (supportive study) in a similar population (N=71) using the same dose and schedule of romidepsin, where the ORR was 34% (CR in 7%) and the median duration of response was 14 months.[68] In the pivotal study, romidepsin also induced clinically significant responses in patients with blood involvement.[69] Among evaluable patients (n=27), the ORR was 32% by composite assessment, including 2 clinical CRs. In a pooled analyses of these two international multicenter clinical studies, objective response

was seen 41% of patients (CR in 7%) in the evaluable population (patients who had at least 2 cycles of romidepsin; n=135).[63] Responses were noted in 42% of patients with stage IIB or greater MF and 58% of patients with SS. Median duration of response and median time to disease progression were 15 months and 8 months, respectively.[63] Romidepsin is approved by the FDA for the treatment of CTCL in patients who have received at least one prior systemic therapy.

Denileukin diftitox is a recombinant fusion protein with interleukin-2 (IL-2) and diphtheria toxin, and targets the high-affinity IL-2 receptor (CD25) expressed on malignant T-cells and B-cells. Although denileukin diftitox was FDA approved for the treatment of patients with persistent or recurrent CTCL based on phase III studies,[70,71] the agent is currently not available (as of June 2012); the manufacturer recently terminated a phase III study in PTCL to prioritize the development of a new improved formulation of the drug.

Conventional cytotoxic systemic chemotherapy is used as a primary treatment only for patients with advanced disease, i.e., stages IIB-IV (see Guidelines page MFSS-A for treatments under "SYST-CAT-B" and "SYST-CAT-C") or large cell transformation (see pages MFSS-6 and MFSS-A for treatments under "SYST-CAT-C") and for second-line therapy for early-stage disease refractory to skin-directed therapies and systemic biologic therapies (see page MFSS-5 for refractory disease). Low-dose methotrexate has been used to treat early-stage MF and SS for many years, although only limited data are available.[72,73] Gemcitabine as a single agent has been evaluated in patients with advanced, heavily pretreated CTCL and as front-line therapy in untreated patients.[74-77] Another nucleoside analog pentostatin has shown activity either as a single agent or in combination with IFN alpha in patients with advanced MF or SS.[78-80] Limited data also suggest some activity for the oral alkylating agent temozolomide and the proteasome inhibitor bortezomib in patients with previously treated MF.[81,82]

Pegylated liposomal doxorubicin has shown substantial single-agent activity in patients with pretreated, advanced or refractory CTCL.[83-85] In a small prospective phase II trial in patients with previously treated CTCL (N=19; MF, n=13 [including transformed MF in n=3]; SS, n=3), pegylated liposomal doxorubicin induced an ORR of 84% (CR in 42%) with no significant differences between patients with stage I-IIA and IIB-IV disease.[84] After a median follow up of 23 months, the median event-free survival and OS was 18 months and 34 months, respectively. In another prospective study in patients with advanced or refractory MF/SS (N=25), the ORR was 56% (CR in 20%) with pegylated liposomal doxorubicin.[85] The median OS was 44 months. A phase II multicenter trial from the EORTC evaluated pegylated liposomal doxorubicin in patients with advanced MF (stage IIB, IVA, IVB) refractory or relapsed after at least 2 prior systemic therapies.(N=49).[86] The ORR was 41% (CR in 6%). The median time to progression was 7 months and the median duration of response was 6 months. Single-agent therapy with pegylated liposomal doxorubicin was well tolerated with no grade 3 or 4 hematologic toxicities; the most common grade 3 or 4 toxicities included dermatologic toxicity other than hand and foot reaction (6%), constitutional symptoms (4%), gastrointestinal toxicities (4%) and infection (4%).[86] A recent phase II study evaluated pegylated liposomal doxorubicin followed sequentially by oral bexarotene in patients with advanced-stage or refractory CTCL (N=37; stage IV, n=21 [including SS, n=7]; stage IIB, n=10; refractory, n=6).[87] Treatment with 8 doses (16 weeks) of liposomal doxorubicin resulted in an ORR of 41% including clinical CR in 2 patients (n=34 evaluable). The maximum response was observed after 16 weeks of treatment with liposomal doxorubicin; sequential bexarotene did not improve the response rate or

duration. At the time of follow up (median 7.5 months for surviving patients), the median PFS was about 5 months.[87]

Pralatrexate is a folate analog indicated for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL), and has also demonstrated activity in patients with CTCL. In a multicenter dose-finding study, pralatrexate 10 mg/m^2 to 30 mg/m^2 (given weekly for 2 of 3 weeks or 3 of 4 weeks) was evaluated in patients with relapsed or refractory CTCL (N=54; MF, n=38 [70%]; SS, n=15 [28%]).[88] Patients had received a median of 4 prior systemic therapies (range, 1–11). The recommended dose was identified as 15 mg/m^2 weekly for 3 weeks of a 4-week cycle. The ORR for all evaluable patients on this study was 41% (CR in 5.5%). Among the patients (in the dose-finding cohort and expansion cohort) who received the recommended dose (as above; n=29), the ORR was 45% (CR in 3%).[88] Thus, low-dose pralatrexate was shown to have high activity in patients with heavily pretreated CTCL.

Based on limited data from clinical studies and case report, liposomal doxorubicin, denileukin diftitox and gemcitabine have shown some activity in patients with transformed MF.[85,89,90] In the subgroup of patients with relapsed/refractory transformed MF (n=12) treated on the PROPEL trial that evaluated pralatrexate (30 mg/m^2 weekly for 6 weeks of a 7-week cycle) in patients with PTCL, the ORR based on investigator assessment and by independent review was 58% and 25%, respectively.[91,92] Based on investigator assessment, the median duration of response was 4 months and median PFS was 5 months. The median OS was 13 months.[91]

Combination therapies

Combinations of biologic or non-cytotoxic therapies as distinct from combination chemotherapies are used when single-agent therapies fail or in cases of advanced, progressive, or refractory disease (see Guidelines page MFSS-A for regimens under "Combination Therapies"). The rationale for such systemic combination strategies in CTCL is to provide synergistic efficacy without additive toxicities. Combinations of systemic agents with skin-directed therapies are often used to maximize clinical responses in the skin compartment. Several combination therapies have been studied in clinical trials for CTCL. Most commonly used combination regimens include phototherapy plus either IFN or systemic retinoid, and ECP plus either IFN or systemic retinoid or both.[93-99] PUVA when used in combination with IFN alfa produced an ORR of 93% (CR in 80%) in patients with stage IB to stage IVB disease evaluated in a phase I trial (N=15); the median duration of response exceeded 23 months.[93] In a prospective randomized study evaluated IFN combined with PUVA versus IFN combined with retinoids in patients with stage I or II CTCL (N=82 evaluable), the combination of IFN with PUVA resulted in significantly higher CR rates in this patient population (70% vs. 38%).[97] In a phase II trial in patients with symptomatic MF/SS (N=63; stages IA-IIA, n=43; stages IIA-IIB, n=6; and stages III-IVA, n=14). IFN combined with PUVA (followed by PUVA maintenance in patients with a CR) resulted in a CR in 75% of patients, with a median duration of response of 32 months.[99] The 5-year DFS and OS rates were 75% and 91%, respectively. In another prospective phase II trial in patients with early-stage MF (stages IA-IIA; N=89), the combination of low-dose IFN alfa with PUVA resulted in an ORR of 98% (CR in 84%).[94] Low-dose bexarotene in combination with PUVA also resulted in high response rates with an ORR of 93% (CR in 47%) in a small group of patients with MF/SS (all stages) resistant or intolerant to previous therapies (N=15).[100] However, a phase III randomized study from the EORTC recently reported no significant differences in outcomes using the combination of bexarotene with PUVA compared with PUVA alone in patients with early stage MF (stage IB and IIA;

N=93).[101] The ORR with the combination was 77% (CR in 31%) compared with 71% (CR in 22%) with PUVA alone; the median duration of response was 5.8 months and 9,7 months, respectively. A trend towards fewer PUVA sessions and lower UVA doses to achieve CR was observed with the combination arm, although the differences were not significant.[101] This trial was closed prematurely due to low patient accrual.

The combination of biologic agents with ECP has been shown to improve response rates in patients with advanced stage CTCL.[53,98,102] In a retrospective study involving patients with advanced CTCL (N=47), ECP with or without biologic agents (i.e., IFN, systemic retinoids, sargramostim) resulted in an ORR of 79% (CR in 26%) with a median OS of 74 months.[98] The median OS in the subgroup of patients with stage III or IV disease with blood involvement was 55 months. The combined modality therapy (ECP with IFN and/or systemic retinoids) resulted in improved response rates (84% vs. 75%) and median OS (74 months vs. 66 months) compared with ECP alone despite poor prognostic features among patients treated with combined modality therapy; these differences in outcomes were not statistically significant, however.[98] In a recent retrospective cohort study of patients with SS (N=98) who received at least 3 months of ECP combined with 1 or more biologic agents (i.e., IFN alfa, systemic retinoid, IFN gamma, and/or GM-CSF), the ORR was 75% with CR in 30% of patients.[102] Most patients on this study received ECP in combination with IFN alfa (89%) and/or systemic retinoids (86%); 30% of the patients were treated with ECP combined with both IFN alfa and systemic retinoids. The 5-year OS rate from time of diagnosis was 55% and the median OS was 65%.[102] The 5-year OS rates for the subgroups of patients with stage IIIB, IVA1, IVA2, and IVB were 80%, 80%, 76%, and 0%, respectively. A higher monocyte percentage at baseline was significantly associated with CR rates.[102]

Systemic retinoids have been studied in combination with other biological response modifiers in patients with advanced disease. The combination of low-dose bexarotene and low-dose IFN alfa was reported to have synergistic activity in a small case series of patients with CTCL (erythrodermic CTCL and follicular MF).[103] In a phase II study in patients with CTCL (N=22; all stages) oral bexarotene (at standard doses; 300 mg/m^2/day for at least 8 weeks) was evaluated in combination with IFN alfa (added in cases of <CR after 8 weeks of bexarotene alone).[104] Among evaluable patients (n=18), the ORR for the combined regimen was 39% (CR in 6%). Although the regimen was well tolerated, response rates were not improved relative to the ORR expected with bexarotene alone.[58,59] The combination of bexarotene and denileukin diftitox is particularly interesting given that bexarotene has been shown to increase CD25 expression in CTCL cells, thereby potentially increasing the susceptibility of T-cells to denileukin diftitox. In a phase I study in patients with relapsed/refractory CTCL (N=14), denileukin diftitox combined with bexarotene resulted in an ORR of 67% (CR in 28.5%).[105] Lastly, combined modality therapy with oral isotretinoin and IFN alfa (followed by TSEBT and maintenance therapy with topical nitrogen mustard and IFN alfa) was evaluated in patients with MF (N=95; stages IA-IIA, n=50; stages IIB-IVB, n=45) in a long-term follow-up study.[106] The ORR was 85% with CR in 60% of patients; the CR rate was 76% among patients with early-stage MF (remission >5 years in 24% of responders) and 40% among those with advanced stage disease (remission duration >5 years in 17%). The median DFS and OS rate for patients with early-stage disease was 62 months and 145 months, respectively. The corresponding endpoints for patients with advanced stage disease were 7 months and 36 months, respectively.

The 5-year estimated OS rate was 94% for patients with early-stage and 35% for advanced-stage MF. Disease stage was the only independent prognostic factor for survival based on multivariate analysis.[106]

NCCN Recommendations Based on Clinical Stage

Primary Treatment

The NCCN Guidelines panel recommends that patients diagnosed with MF/SS be treated at specialized centers with expertise in the management of this disease. It should be noted that unlike other NHL subtypes, response criteria for MF/SS has not been shown to correlate with prognosis. The decisions to continue with or switch treatment regimens are often made based on clinical parameters. A proposal for detailed response criteria for MF/SS, according to consensus from an international group of experts, was recently published.[21]

Patients with stage IA disease have an excellent prognosis using skin-directed therapies alone, where their life expectancy is not altered compared with matched control populations.[8,12] Stage IA is managed primarily with skin-directed therapies, alone or in combination with other skin-directed therapies including local RT (see page MFSS-4). Local RT (12–36 Gy) is recommended particularly for unilesional presentation. Treatment options include topical corticosteroids, topical chemotherapy (i.e., nitrogen mustard or carmustine), topical retinoids (i.e., bexarotene or tazarotene), topical imiquimod, and/or phototherapy (UVB for patch or thin plaques; PUVA for thicker plaques) (see page MFSS-A). Patients with a PR to initial therapies (i.e., having persistent T1 skin disease) should be treated with other options from the list of recommendations therapies mentioned above.

Patients with stage IB-IIA disease require generalized skin treatment (see page MFSS-5). Topical retinoids are not recommended for generalized skin involvement because these treatments can cause substantial irritation. In addition to the other skin-directed therapies used for stage IA disease (as mentioned above), TSEBT (12–36 Gy) is another treatment option for those with severe skin symptoms or generalized thick plaque or tumor disease (see page MFSS-A. Although TSEBT is highly effective in T1 disease (stage IA), it is reserved for generalized or recalcitrant skin disease due to its toxicities and lack of superior long-term outcome. It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response. For patients with sites that are not responsive to generalized treatment, additional treatment may be needed. Patients with persistent T1 skin disease should be treated with skin-directed therapies as mentioned for patients with stage 1A disease; patients with persistent T2 disease should be treated with other options from the list of treatments for generalized skin involvement, as mentioned above.

Patients with early stage disease (stage IA, stage IB-IIA) with B1 blood involvement are often best managed with more intensive treatments as described for stage III with B1 blood involvement (see Discussion below). Patients with histological evidence of folliculotropic or large cell transformation (LCT) are usually managed as described for treatment of stage IIB disease (see Discussion below).

Patients with stage IIB disease and/or histological evidence of folliculotropic or LCT can be separated into two categories: 1) limited extent tumor disease with or without patch/plaque disease; or 2) generalized tumor disease, transformed and/or folliculotropic disease (see page MFSS-6). In patients with tumor disease, rebiopsy is necessary if LCT is suspected. Patients with limited extent tumor disease can be managed with local RT for tumor lesions. Combination or adjuvant systemic therapy (SYST-CAT A: retinoids, IFNs, HDAC inhibitors, ECP, methotrexate [≤100 mg per week]) may be considered

to improve overall response and duration of response. Skin-directed therapies, as described above for stage I-IIA disease, can be used for residual patch or plaque lesions.

Patients with generalized tumor disease are treated with TSEBT or systemic therapy, with or without skin-directed therapy. For patients treated with TSEBT, adjuvant therapy with systemic therapies (SYST-CAT A) can be considered to improve response duration. For systemic therapy, recommended options include treatments listed under SYST-CAT A (as listed above), SYST-CAT B (first-line: liposomal doxorubicin, gemcitabine; second-line: chlorambucil, pentostatin, etoposide, cyclophosphamide, temozolomide, methotrexate [>100 mg per week], bortezomib, low-dose pralatrexate), or SYST-CAT C (liposomal doxorubicin, gemcitabine, romidepsin, low-dose or standard-dose pralatrexate, regimens recommended for PTCL in the NHL Guidelines), or combination therapies.

Systemic therapy is the initial treatment for patients with LCT (see pages MFSS-6 and MFSS-A). If there is no evidence of aggressive growth, systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should initially be considered for options under SYST-CAT A before resorting to treatment options listed under SYST-CAT B or SYST-CAT C. For LCT with aggressive growth, the NHL Guidelines panel recommends systemic therapy with options listed under SYST-CAT C). Combination regimens are generally reserved for patients with relapsed or refractory or extracutaneous disease. Following completion of primary therapy, patients with persistent T1 or T2 disease should be treated with skin-directed therapies for limited (T1) or generalized (T2) skin involvement. Patients with persistent T3 limited extent disease should continue to receive local RT with adjuvant systemic therapy (SYST-CAT A), or systemic therapy (with or without skin-directed therapies and with or without RT). Patients with persistent T3 disease should continue to receive TSEBT, systemic therapies, or combination therapies, with or without skin-directed therapies.

Management of patients with stage III disease depends on the extent of blood involvement (see page MFSS-7): no significant blood involvement (B0) or some blood involvement (B1), which is less than that observed for SS (B2). Patients with no significant blood involvement are treated with generalized skin-directed therapies similar to those recommended for stage IB -IIA (see page MFSS-A). Generalized skin-directed therapies should be used with caution in patients with stage III disease, as treatments other than topical steroids may not be well tolerated. Phototherapy (PUVA or UVB) or TSEBT may be used successfully in these patients. ECP may be a more appropriate systemic therapy for patients with stage III disease with blood involvement. Alternative options include other treatment options listed under SYST-CAT A, with or without skin-directed therapy. Mid-potency steroids should be used in combination with systemic therapy to reduce skin symptoms. Antibiotic therapy should be considered for this group of patients since they are at increased risk of developing secondary infections. Patients with inadequate response or persistent disease should be treated with other options within the list of primary treatments (generalized skin-directed treatments or for blood involvement, SYST-CAT A with or without skin-directed therapy).

Stage IV disease includes SS and non-Sézary or visceral (solid organ) disease. SS patients are treated with single agent systemic therapy (agents listed in SYST-CAT A) or combination therapies (see pages MFSS-8 and MFSS-A). Safety data on the use of systemic retinoids in combination with TSEBT and vorinostat in combination with phototherapy or TSEBT is currently lacking. Non-Sézary or solid organ disease is frequently managed with systemic therapy (SYST-CAT B or

SYST-CATC) with or without RT for local control. These patients may present with more aggressive growth characteristics. If there is no evidence of aggressive growth, systemic therapies from SYST-CAT B would be more appropriate. In cases where aggressive growth is observed, the regimens listed under SYST-CAT C would be preferred. Adjuvant biologic therapy may be considered following chemotherapy to improve response duration.

All patients (stage IA through stage IV) showing response (and/or clinical benefit) should be considered for maintenance or tapering therapy to optimize response duration. Patients with a PR or disease relapse following primary treatment should be treated with the other options included in the primary treatment to improve response before starting treatment for refractory disease. In addition, patients with disease relapse or persistent disease may be considered for clinical trials. Patients with stage IV disease should be considered for clinical trials.

Refractory, Progressive, or High-Risk/Advanced Disease

Role of Allogeneic Stem Cell Transplantation

Autologous stem cell transplantation (SCT) has been used infrequently for patients with CTCL. In general, the duration of response have been short, thus limiting its utility and uptake.[107] Allogeneic SCT has been reported only in case reports or small series in patients with advanced MF and SS,[107-111] or in retrospective studies.[112-114] Several of these published cases reported on the association between graft-versus-host-disease and tumor response, or the reinduction of remission following withdrawal (or reduction) of immunosuppression, suggesting that graft-versus-tumor effect may play an important role in the extent of disease control achieved with allogeneic SCT.[108,109,111-113] A meta-analysis compared the outcome of allogeneic versus autologous SCT in patients with MF and SS based on patient cases derived from the literature (N=35).[115] The analysis suggested that OS outcomes and response durations were more favorable among the patients who received allogeneic SCT.[115] In the allogeneic SCT group, the majority (70%) of patients experienced persistent graft-versus-host disease (GVHD), which was primarily mild to moderate in severity. Whereas the majority of the deaths among patients undergoing autologous SCT may be attributable to progressive disease,[115] deaths associated with allogeneic SCT may be more due to non-relapse mortality (NRM). The incidence of NRM in published reports with allogeneic SCT is about 21% to 25%.[112-114] In a study that evaluated TSEBT with allogeneic HSCT in patients with advanced CTCL (N=19), the ORR was 68% (CR in 58%) with median OS not reached at the time of the report; the TRM rate was 21%.[113] In a retrospective analysis of patients with MF/SS registered in the EBMT database (N=60), the 3-year PFS and OS rate with allogeneic SCT was 34% and 54%, respectively.[112] The NRM rate at 2 years was 22%. Outcomes were not significantly different between histology types. However, patients with advanced-stage disease had a higher 3-year relapse rate compared with those with earlier stage disease (53% vs. 25%; *P*=0.02). The use of reduced-intensity conditioning was associated with significantly lower 2-year NRM rate (14% vs. 49%; *P*=0.021) and higher 3-year OS rate (63% vs. 29%; *P*=0.019) compared with myeloablative conditioning; the relapse rate at 2 years was not different between these subgroups. In addition, transplantation from matched related donors was also associated with significantly lower NRM rate (16% vs. 40%; *P*=0.035) and higher OS rate (63% vs. 24%; *P*=0.001) compared with transplantation from unrelated donors.[112] Allogeneic SCT appears to be a promising therapeutic strategy in patients with advanced CTCL. Further data from prospective studies are needed to establish the role of allogeneic SCT in these patients.

Alemtuzumab

Alemtuzumab, a humanized anti-CD52 monoclonal antibody, has shown promising activity in patients with advanced MF and SS.[116-121] In studies using standard dose alemtuzumab (IV or SC; 30 mg thrice weekly for up to 12 weeks) in heavily pretreated patients with advanced MF or SS, the ORR was 38% to 84% (CR in 0–47%); most patients progressed within 4 to 6 months.[116,121,122] In a phase II study in patients with advanced MF/SS (N=22; stage III-IV in 86%; median 3 prior therapies), the ORR with single-agent alemtuzumab was 55% (CR in 32%).[116] The median time to treatment failure (in responding patients) was 12 months. In a recent study of alemtuzumab in heavily pretreated patients with relapsed/refractory erythrodermic MF and SS (N=19), the ORR was 84% (CR in 47%); median PFS and OS was 6 months and 41 months, respectively.[122] Major toxicities with alemtuzumab included myelotoxicities and infectious complications (including those attributed to cytomegalovirus reactivation), thus prompting the investigation of lower doses of alemtuzumab.[118,119] In a study of patients with SS (N=14; relapsed/refractory SS, n=11), SC alemtuzumab at low doses (3-15 mg per administration) given for a short time period based on Sézary cell count, was associated with an ORR of 86% (CR in 21%) with an acceptable toxicity profile.[118] The median time to treatment failure was 12 months. None of the patients who received the 10 mg dose developed hematologic toxicities or infections, which suggested that low-dose alemtuzumab (up to 10 mg per dose) may be a reasonable regimen for patients with pretreated SS.

Management of Relapsed, Progressive Stage IA-IIB Disease

Clinical trial participation or systemic therapy with agents listed under SYST-CAT A, as single agent or combination therapy, is recommended for patients with stage IA, IB-IIA disease that is progressive or refractory to primary skin-directed therapies (see page MFSS-5). Skin-directed therapy can be used as adjuvant treatment to reduce skin symptoms. Patients who do not respond to treatment with agents under SYST-CAT A should be considered for clinical trial, TSEBT (if not previously administered) or in the absence of a suitable clinical trial, treated with single agent systemic chemotherapy with regimens listed under SYST-CAT B.

In patients with refractory or progressive stage IIB disease with limited-extent tumor disease (with or without patch/plaque), options may include those used as primary treatment for stage IIB generalized extent tumor disease (see page MFSS-6); these options include TSEBT (with or without adjuvant systemic therapy from SYST-CAT-A to improve response duration), systemic chemotherapy, or combination therapies—with or without skin-directed therapies. In patients with stage IIB disease refractory to or progressive with these treatment options, options may include multiagent chemotherapy, consideration for allogeneic SCT or clinical trial participation. Patients are generally treated with multiple agents from SYST-CAT A or SYST-CAT B or with combination therapies before receiving multiagent chemotherapy.

Management of Relapsed Stage III or High-Risk Disease

In patients with refractory or progressive stage III disease, combination therapy or clinical trial should be considered (see page MFSS-7); if the patient remains refractory or progresses during second-line therapy, then clinical trials, systemic therapy with agents listed under SYST-CAT B, or allogeneic SCT (including options using non-ablative conditioning) may be considered. Alemtuzumab may also be considered in this setting. For patients with stage IV/SS or non-Sézary disease with relapse (following a response) or persistent disease (inadequate response), allogeneic SCT may be considered, as appropriate. For patients with refractory or progressive SS (non-response to primary treatment), systemic therapy with agents listed under SYST-CAT B,

alemtuzumab, or clinical trial participation would be appropriate options. For patients with refractory or progressive non-Sézary or visceral disease, clinical trials should be considered.

Considerations for Allogeneic SCT

As mentioned above, allogeneic SCT may be considered for patients with stage IIB-IV disease that is progressive or refractory to primary treatment options. Appropriate patients (stage IIB or stage III MF who have failed multiple systemic therapies/combination therapies and adequate trial of skin-directed therapy; high-risk stage IV patients with relapse or inadequate response following primary treatment with systemic therapies, combination therapies and/or multiagent chemotherapy) may be referred for a transplant consultation. In general, patients should have failed biologic options and single agent chemotherapy prior to allogeneic SCT. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant. Patients with relapsed/progressive disease only in the skin should not be referred for transplant. The ideal timing for allogeneic SCT is when the disease is well controlled with induction therapy and before the disease has progressed to a state where the chance of response or survival with allogeneic SCT is low. This is particularly true for patients with high-risk stage IV disease that has relapsed (or has persistent disease) after primary treatment. For these patients, consideration of allogeneic SCT should be made earlier in the treatment phase to optimize response to induction therapy prior to transplant. Thus, for high-risk stage IV disease, allogeneic SCT should not be a 'last resort' option.

Currently there is no definitive treatment for advanced disease that can produce reliable durable remissions or curative results, other than possibly, allogeneic SCT. The NCCN Guidelines recommend participation in a clinical trial as a treatment option for all patients with relapsed or progressive disease.

Supportive Care for Patients with MF/SS

Management of Pruritus

Symptoms of pruritus can be present in a large majority (nearly 90%) of patients with CTCL, and may be associated with decreased quality of life for patients.[123,124] Patients with MF/SS should be evaluated for pruritus at each visit. Other potential causes of pruritus (e.g., contact dermatitis, atopic dermatitis, psoriasis, other inflammatory skin conditions) should be ruled out. The extent of pruritus should be determined (localized vs. generalized), and potential correlation between disease site and localization of pruritus should be noted. Daily use of moisturizers and emollients are helpful in maintaining and protecting the skin barrier. The treatment of pruritus requires optimizing skin-directed and systemic treatments. Topical steroids (with or without occlusion) can be effective in managing the disease and accompanying pruritus in early-stage disease. [125,126] First-line options with systemic therapies include antihistamines, the tricyclic antidepressant doxepin or the anticonvulsant gabapentin.[125,127] In the second-line setting, systemic therapy with the neurokinin-1 receptor antagonist aprepitant, the tetracyclic antidepressant mirtazapine or use of selective serotonin reuptake inhibitors may be considered.[125,127-129] Treatment with the oral opioid receptor antagonist naltrexone may be considered if symptoms of pruritus do not resolve with the above agents.[130-132]

Prevention and Treatment of Infections

Infectious complications are frequent among patients with MF/SS, particularly cutaneous bacterial infections and cutaneous herpes viral infections (e.g., HSV or HZV infections).[133] Bacteremia/sepsis and bacterial pneumonia were reported as the major cause of death due to

infections in a retrospective cohort study of patients with MF/SS.[133] Several preventive measures can be incorporated to minimize infectious complications in patients with MF/SS. These measures include maintaining/protecting the skin barrier (routine use of skin moisturizers and/or emollients), bleach bath or soaks (for limited areas only), avoidance of central lines (particularly for erythrodermic patients) and prophylactic use of mupirocin in cases of *Staphylococcus aureus* (*S. aureus*) colonization. Patients with MF/SS undergoing treatment with alemtuzumab-containing regimens should be closely monitored for cytomegalovirus (CMV) reactivation and preemptively treated with antivirals to avoid overt CMV disease (see Guidelines section for Supportive Care for NHL).

For active or suspected infection in patients with erythroderma, cultures from skin swab and nares (nostrils) should be taken to evaluate for *S. aureus* colonization/infection. Bleach baths or soaks may be helpful if the affected area is limited. Antimicrobial treatments may include intranasal mupirocin and/or oral dicloxacillin or cephalexin. For cases of suspected methicillin-resistant *S. aureus* (MRSA) infection, trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline should be considered. If no improvements in infection status are observed with the above agents, or if bacteremia is suspected, vancomycin should be initiated. Further information on the appropriate use of vancomycin is included in the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections (also available at nccn.org).

Infection with Gram-negative rods is common in necrotic tumors, and may lead to serious complications such as bacteremia/sepsis. For active or suspected infections in patients with ulcerated and necrotic tumors, blood cultures should be obtained and empiric therapy with antibacterials should be considered even in the absence of a fever. An antimicrobial agent with broad-spectrum coverage (including coverage for both Gram-negative rods and Gram-positive cocci) should be chosen initially. The role of skin/wound culture is not clear in this setting. Further information on empiric therapy in cancer patients at risk for infections is included in the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections (at nccn.org).

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