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SPECIAL ARTICLE

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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

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ABSTRACT

Mycosis fungoides (MF) and Sézary syndrome (SS), the major forms of cutaneous T-cell lymphoma, have unique characteristics that distinguish them from other types of non-Hodgkin's lymphomas. Clinical trials in MF/SS have suffered from a lack of standardization in evaluation, staging, assessment, end points, and response criteria. Recently defined criteria for the diagnosis of early MF, guidelines for initial evaluation, and revised staging and classification criteria for MF and SS now offer the potential for uniform staging of patients enrolled in clinical trials for MF/SS. This article presents consensus recommendations for the general conduct of clinical trials of patients with MF/SS as well as methods for standardized assessment of potential disease manifestations in skin, lymph nodes, blood, and visceral organs, and definition of end points and response criteria. These guidelines should facilitate collaboration among investigators and collation of data from sponsor-generated or investigator-initiated clinical trials involving patients with MF or SS.

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INTRODUCTION

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common variants of cutaneous T-cell lymphoma (CTCL).[1-3] The prognosis of MF and SS depends on the type and extent of skin lesions and extracutaneous disease,[4] which were first captured in the TNM classification published for CTCL in 1979.[5] Suggested modifications published in 2007 for MF/SS[1] (Tables 1 and 2) revised the nodal clinicopathologic classification, added blood involvement to the staging of MF/SS, and removed the ambiguity surrounding variables critical to a standardized staging and classification system.

The final barrier to collaborative clinical trials of MF and SS is the lack of standardized end points and response criteria. Standardization would facilitate: (1) the approval of effective new treatments for MF/SS by expediting protocol development and review; (2) consolidation or comparison of data on a given therapy for MF/SS collected at multiple sites and/or at different time points; and (3) comparison of efficacy results of various therapeutic agents for MF/SS evaluated in different clinical trials.

From eight workshops held in 2004 to 2009, the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) developed the following consensus guidelines to resolve this deficiency. These guidelines include: recommendations for standardizing general protocol design; a scoring system for assessing tumor burden in skin, lymph nodes, blood, and viscera; definition of response in skin, nodes, blood, and viscera; a composite global response score; and a definition of end points.

Table 1. Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS[1]

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node†	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/μL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; NCI, National Cancer Institute.

*Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

†Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions[1] to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.

‡The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

STUDY DESIGN

For all clinical trials in MF/SS, the following is recommended[6]:

1. The definition of patch, plaque, and tumor should be as outlined in Table 1.

Table 2. Modified ISCL/EORTC Revisions to the Staging of MF/SS[1]

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

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; X, clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.

2. For study eligibility, the histopathologic diagnosis should be confirmed in a skin biopsy representative of current disease by a pathologist with expertise in cutaneous lymphoma. For SS (defined as meeting T4 plus B_2 criteria[1]), where the biopsy of erythrodermic skin may only reveal suggestive but not diagnostic histopathologic features, the diagnosis may be based on either a node biopsy or fulfillment of B_2 criteria[1] including a clone in the blood that matches that of the skin. For early patch stage MF where the histological diagnosis by light microscopic examination is not confirmed, diagnostic criteria that have been recommended by the ISCL should be used.[6] A biopsy performed at baseline (pre-entry) is preferred as it reflects the current status of disease, may be necessary to assess histologic findings included in the inclusion/exclusion criteria, may give information on

Table 3. Modified Severity Weighted Assessment Tool

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

NOTE. mSWAT score equals summation of each column line.

Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.

*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.

†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

prognosis (eg, large cell transformation or folliculotropism) that is unanticipated and important for stratification of cohorts in a randomized controlled trial (RCT), and provides adequate tissue for any additional correlative studies. However, a prior tissue specimen can be used for diagnostic purposes provided that the type of lesion biopsied is representative of current skin lesions, the study pathologist finds it meets the current criteria for MF/SS, it provides sufficient information for all inclusion/exclusion and stratification purposes, and the patient has not experienced progressive disease since the biopsy was performed. All skin biopsies should be done after a time period off any therapy that may affect the histologic interpretation or diagnostic criteria important to the clinical trial—this primarily affects patch lesions and 2 to 4 weeks off therapy generally suffices.

3. If subjects are enrolled onto an RCT with clinical or histologic variants of MF (eg, hypopigmented MF, granulomatous slack skin, folliculotropic MF) or with other than skin histopathologic criteria for study entry, consideration should be given to stratification of treatment groups and separate reporting of study results for these variants.

4. There should be a wash-out time period from any treatment likely to affect the course of MF/SS and therefore the inclusion/exclusion criteria or the subsequent assessment of the efficacy and safety of the study treatment. Although a 4-week wash-out period is recommended for most participants in order to minimize any latent clinical benefit or residual toxicity from the prior treatment, this time period is best determined based on the biologic effects of the therapy and whether the patient is experiencing progressive disease despite ongoing treatment.

5. An exception to concurrent therapy with proven efficacy in MF/SS is topical or systemic steroids in those patients with erythroderma who have been on corticosteroids for prolonged periods of time and where discontinuation may lead to rebound flare in disease, adrenal insufficiency, and/or unnecessary suffering. In these cases, the continued use during the trial of either low-dose systemic steroid (equivalent to $\leq$ 10 mg per day of prednisone) or low potency topical steroids may be considered if the frequency and dosage of either has been constant for a period of time before the study and will remain constant until improvement occurs at which time dosage may be decreased. However, no complete response (CR) can be ascribed to a study drug while a patient remains on concomitant therapy with known efficacy in MF/SS (including topical or systemic steroids), but rather the maximum response to study drug would be a partial response (PR). Those patients in whom a PR was achieved only while on combination therapy with any such agent should be so noted in the final study report.

6. RCTs that utilize a control group of similar patient characteristics and prior treatments and who are being treated with a therapeutic agent previously shown to have efficacy in this disease remain the ideal and a goal that cooperative studies in MF/SS may help to meet. The utilization of historical controls is suboptimal as there is the potential for underestimation of the response rate of controls,[7] and specifically in MF/SS, a difference in the diagnostic or entrance criteria and/or prior treatments utilized in the current and comparative groups.

7. For the purposes of determining enrollment eligibility and/or stratification of treatment groups, the maximum TNMB staging reached as well as the current disease activity (global score) at entry should be considered. This will help ensure that information important to outcome/prognosis is available at study onset and considered in any trial results.

8. It is important for purposes of TNMB assignment that before a patient enters a clinical trial, any abnormal lymph node be characterized histologically. An excisional biopsy of a representative enlarged or otherwise abnormal peripheral node is recommended to determine the architectural changes that characterize the $N_{1\text{-}3}$ histologic categories.[1] However, this type of biopsy carries the risks of infection, bleeding, and lymphedema, and repetitive excisions in the same nodal region are to be avoided. Therefore, the most recent excisional biopsy of a representative abnormal lymph node may be used for baseline nodal classification as long as there has been persistent and stable lymph node enlargement and, in the case of $N_{1\text{-}2}$ classification on prior biopsy, stable lymph node size since the time of that biopsy even if there have been multiple treatments since the last node biopsy.

9. The frequency of direct patient assessment in a given protocol should take into account the specifics of the type and schedule of treatment and the patient's TNMB status. Where the duration of a given treatment effect is to be determined or where the response duration is being tracked as an end point in the trial, follow-up at least monthly is recommended to avoid overestimation of the duration of the effect/response. The frequency of the assessment of lymph node, viscera, and/or blood involvement by other than physical examination should be determined by the patient's TNMB status, the response in skin, and the need/desire to assess global response.

10. The pretreatment evaluation and scoring of response parameters should be done at baseline (day 1 of treatment), and not at screening. These scores will constitute the comparison values for all response measurements during the study.

11. All responses should be documented to be at least 4 weeks in duration: an objective response (CR or PR) for a lesser period of time is of questionable value and runs the risk of being unrelated to the study drug (eg, improvement while on a course of antibiotics). In cases where the definition of progressive disease (PD) or relapse is met but the clinical impression is questionable, documentation for a period of at least 4 weeks is also recommended to avoid a patient being removed prematurely from the study.

12. To be consistent with that of other NHLs, the definition of PD during a clinical trial of patients with MF/SS would include both nonresponders who meet the definition of PD and responders who meet the definition of loss of response. It is acknowledged that a loss of response in responders (PR plus CR) and/or a relapse in those patients with a CR may have different prognostic implications than PD in nonresponders and that the precise definition of PD used in any given trial should be reported.

13. The duration of a given study should be long enough to ensure that a significant response is able to occur and that it is sustained. If time to an event is also a goal (such as time to PD), then routine evaluation off therapy may be indicated.

14. Primary statistical analysis in an efficacy trial should be based on the intention-to-treat population.

SKIN ASSESSMENT, SCORING, AND DEFINITION OF RESPONSE

Skin Assessment and Scoring

Total body skin scoring. The most widely used method for skin scoring is the Severity Weighted Assessment Tool (SWAT)[8,9] or its

modification, the mSWAT.[10] This technique involves the direct assessment of the body-surface area (BSA) of each type of MF/SS lesion (palm plus fingers of the patient = approximately 1% BSA) in each of 12 areas of the body, multiplying the sum of the BSA of each lesion type by a weighting factor (patch = 1, plaque = 2, and tumor = 3 or 4) and generating a sum of the subtotals of each lesion subtype (Table 3; Appendix Fig A1, online only).

There has been much discussion about the appropriate weighting factor for tumors given their prognostic importance. The thickness of the dermal infiltrate of tumors in MF[11] is far greater than 4 times that of patches (the current weighting factor for tumors in the mSWAT score) as is the proportion of neoplastic cells. As currently constructed in the mSWAT, any change in tumor size or number will be underrepresented in the total mSWAT compared to changes in patch and plaque lesions. However, the variability of investigators in assigning a lesion to plaque versus tumor is quite high (unpublished data, E. Vonderheid, 2003; unpublished data, E. Olsen, 2006), which complicates the simple remedy of increasing the weighting factor of tumor versus patch/plaque and underscores the importance of a single assessor during a clinical trial.

It would be ideal if the same scoring system could be used for both MF and SS. Methods that have been employed to track response in SS and erythrodermic MF in clinical trials and their relative benefits and drawbacks are presented in Table 4.[9,10,12] Although not specifically previously noted, the mSWAT can be utilized to track erythroderma by the summation of BSA involved with patch disease (macular erythema) and plaque disease (erythema with induration/edema) while maintaining the ability to simultaneously track any tumors that may be present. Patients assigned the diagnosis of erythrodermic MF or SS should fulfill the ISCL criteria of erythroderma (T_4 skin classification; ie, BSA $\geq$ 80% erythematous patch/plaque disease).[13]

Standardized photographs of the skin are recommended to document the appearance of skin lesions at baseline and at times of response/progression.

Local/or index/target lesion skin scoring. There are circumstances where local index lesion skin scoring is particularly useful in determining the effectiveness of a treatment for MF, such as in studies targeting some but not all lesions or where it is desirable to monitor the effect of treatment to only one type of lesion. One such method of index lesion scoring for patch/plaque disease is the Composite Assessment of Index Lesion Severity (CA or CAILS; Table 5).[14] Another simpler method of local skin scoring is to determine the sum of the area of each target lesion multiplied by the weight assigned to the lesion type (ie, patch = 1, plaque = 2, tumor = 4 as with mSWAT); this eliminates the CAILS pigmentation severity score and the potential over- or underestimation in the BSA that may be seen with the CAILS. Tumors may be tracked by either utilizing the tumor column of the mSWAT score or by the summation of the area $\times$ height for each tumor (index or all lesions).

Table 5. Composite Assessment of Index Lesion Severity

Clinical Sign and Degree or Size (scale of 0-8)	Index Lesion				
	1	2	3	4	5
Erythema					
Scaling					
Plaque elevation					
Hypo- or hyperpigmentation					
Lesion size*					
Subtotal					
Total (sum of subtotals)					

NOTE. Cannot be used as skin assessment in global response score. Suggestions for improvement include using actual size of lesion versus categorical score for size and eliminating pigmentation as a clinical parameter.
*Lesion size (cm^2): 0: no measurable area; 1: $>$ 0 to $\leq$ 4; 2: $>$ 4 to $\leq$ 10; 3: $>$ 10 to $\leq$ 16; 4: $>$ 16 to $\leq$ 25; 5: $>$ 25 to $\leq$ 35; 6: $>$ 35 to $\leq$ 45; 7: $>$ 45 to $\leq$ 55; 8: $>$ 55 to $\leq$ 70; 9: $>$ 70 to $\leq$ 90; 10: $>$ 90 to $\leq$ 110; 11: $>$ 110 to $\leq$ 130; 12: $>$ 130 to $\leq$ 155; 13: $>$ 155 to $\leq$ 180; 14: $>$ 180 to $\leq$ 210; 15: $>$ 210 to $\leq$ 240; 16: $>$ 240 to $\leq$ 270; 17: $>$ 270 to $\leq$ 300; 18: $>$ 300.

There are, however, inherent problems with any index scoring system being used as the sole skin score for MF/SS: these methods make it possible to record a CR in the situations where all target lesions clear even if nonindex/nontarget lesions persist or even progress or where new lesions outside the index/target lesions appear and are not responsive to therapy. Given that a global score should include an assessment of the entire skin surface, local index/target lesion scoring should not be used in a global scoring system for MF/SS.

Definition of Response in Skin

It is recommended that the mSWAT in a given clinical trial be performed at the bedside by the same investigator at all time points to eliminate inter-observer variability for a given patient. If the same investigator cannot perform all the assessments, then all personnel grading the same patient must have completed prior training, ideally before study initiation.

Table 4. Methods of Assessment of Erythroderma Used in Various Clinical Trials of MF/SS

Reference	Method	Comments
Edelson et al[12]	Percent skin involvement in various body regions multiplied by a 0-4 point severity scale that includes degrees of erythema, edema, exfoliation, fissuring, and induration	Severity factors not considered individually
Olsen et al[9]	Specific erythroderma scale that includes both extent and severity of involvement	A minor change in severity can profoundly affect the overall score
Olsen et al[10]	Visual analog scale of 0-10	Global physician score that combines extent with severity but does not define specifics of either
This article	Patch plus plaque sections of mSWAT score; sum of BSA involved with patch disease $\times$ weighting factor of 1 plus plaque disease $\times$ weighting factor of 2	No additional work if already performing mSWAT; does not track fissures or scale/exfoliation separately

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome.

Table 6. Response in Skin

Response	Definition
Complete response	100% clearance of skin lesions*
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease†	≥ 25% increase in skin disease from baseline or New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

NOTE. Based on modified Severity Weighted Assessment Tool score.
*A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides[7]), the response should be considered a partial response only.
†Whichever criterion occurs first.

The definition of response in skin of patients with MF/SS is as presented in Table 6. Absence of T-cell receptor (*TCR*) gene rearrangement clonality in the skin as additional evidence of clearing[15] has not been validated for use in clinical trials.

LYMPH NODE ASSESSMENT, SCORING, AND DEFINITION OF RESPONSE

Physical examination alone is an unreliable method for determining the size of peripheral lymph nodes[16] and is inadequate to assess involvement of internal organs. Therefore, when it is important to fully characterize the TNMB status of participants and to be able to make an assessment of global response during a clinical trial, computed tomography (CT) imaging is recommended to be used with the caveat that considerable inter-observer variability exists even for CT scans.[17] However, a concern that is now gaining attention is the radiation exposure associated with different imaging studies. For example, a single abdominal CT scan versus a PA and lateral chest x-ray exposes the patient to approximately 0.01 Gy compared with 0.000015 mGy radiation respectively.[18] An [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography (PET) scan gives additional information on the likelihood of involvement by lymphoma but may have false positive results with infection or inflammation[19] and essentially doubles the radiation exposure and cost of a CT scan. Given the likelihood that many patients with MF/SS will undergo multiple CT scans during their lives, the number of CT or FDG-PET/CT scans during individual clinical trials should be minimized.

In clinical trials of patients with MF/SS in whom global response is to be determined, it is recommended that CT scans be performed at screening/baseline in all patients. In those patients with clinically early disease (maximum/current $T_{1-2}N_0M_0B_{0-1}$), repeat scans are not recommended except in cases of an objective response (OR) in the skin where this is necessary for determination of global response or if there is a suggestion of new nodal or visceral involvement. In those patients with more advanced disease at baseline (maximum/current TNMB greater than $T_{1-2}N_0M_0B_{0-1}$), repeat imaging studies should be performed at the time of PR and CR in the skin; any time there is a question of new or PD in the lymph nodes or viscera; and at end of study. Although FDG-PET scans may be useful to corroborate a CR in the nodes or viscera in patients with other forms of NHL,[19] the limited data on FDG-PET scans in MF/SS, the additional radiation, the cost of sequential FDG-PET scans, and the difficulty distinguishing tissue inflammation from that related to lymphoma in MF/SS do not warrant its routine use as an assessment tool in clinical trials of MF/SS at this time.

Magnetic resonance imaging is an alternative to CT that gives accurate information on the size of lymph nodes and viscera without radiation exposure, but it is costly and its use is limited in patients with compromised renal function. While ultrasound would seem a desirable method to evaluate peripheral lymph nodes, given that bidimensional measurements are possible without ionizing radiation, unfortunately there is a lack of consistent repetitive measurements based on the variability in imaging planes and the entire examination cannot be reproduced for independent review at a later time point.

A repeat peripheral lymph node biopsy during a clinical trial is only recommended in situations where the histology would affect the global response score. Examples include when a patient without abnormal nodes at baseline develops new lymphadenopathy of unclear etiology or when a patient with known lymphomatous involvement (N_3) of a peripheral lymph node that was ≤ 1.5 cm in the long axis or < 1 cm in the short axis has a persistent lymph node larger than 1 cm in diameter in the short axis. Although a repeat excisional biopsy is preferred, to avoid possible morbidity, consideration should be made as to whether either a fine needle aspirate or core biopsy with supportive ancillary studies such as flow cytometry and/or molecular TCR gene analysis in addition to cytology may suffice for response assessment. Any equivocal or absent pathologic assessment of an abnormal lymph node should be considered N_x and not considered for a designation of CR. All other assessments of peripheral node response during a clinical trial would be by the sum of the product of the longest bidimensional diameters (SPD) of the lymph nodes seen on CT (ie, by size alone).[19]

Central lymph nodes were not previously addressed in MF/SS staging because they are generally only seen in late disease when other extracutaneous sites are also involved and are not easily amenable to biopsy confirmation. However, modifications to the 2007 revisions to the staging and classification of MF/SS have been made (Table 1). If there is evidence of enlarged central nodes (defined as > 1.5 cm diameter in the long axis or > 1.0 cm diameter in the short axis), and confirmation of involvement with MF/SS by biopsy (ie, excisional, fine needle aspirate, or core biopsy), then all central nodes should be tracked thereafter in the same way as peripheral nodes (product of the longest bidimensional measurements of all enlarged nodes).

The definition of response in lymph nodes is given in Table 7.

VISCERAL DISEASE ASSESSMENT, SCORING, AND DEFINITION OF RESPONSE

Biopsy confirmation at baseline is recommended for all forms of visceral disease except for liver and spleen involvement, which may

Table 7. Response in Lymph Nodes*

Response	Definition
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD†	≥ 50% increase in SPD from baseline of lymph nodes or Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.
*Peripheral and central lymph nodes.
†Whichever criterion occurs first.

Table 8. Response in Viscera

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD*	> 50% increase in size (SPD) of any organs involved at baseline or New organ involvement or Loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.
*Whichever criterion occurs first.

be diagnosed by imaging studies.[1] It is unclear whether bone marrow involvement in MF/SS should be considered as visceral disease or if it represents an additional prognostic factor in patients with SS. However, many investigators consider bone marrow involvement in MF/SS to be an extension of blood involvement (B_2) and not visceral disease, and hence, bone marrow aspirate/trephine biopsies are not considered obligatory for either evaluation or response assessment.

There may be limitations in corroborating a CR in viscera by CT alone[20,21] and in those cases, a confirmatory biopsy may be necessary or lacking this, no CR assessment can be made.

Definition of response in viscera is given in Table 8.

BLOOD ASSESSMENT, SCORING, AND DEFINITION OF RESPONSE

While a variety of measures for defining blood involvement for staging has utility in clinical practice, tracking blood involvement in clinical trials requires use among all participating centers of a single method that both defines and quantifies blood neoplastic cells including insignificant or absent blood involvement. Currently, this will require consideration of additional definitions of B_0 and B_2 for the purpose of clinical trials that are outside those used for staging purposes alone. The prognostic implications, benefits, and drawbacks of the various current methods of quantification of neoplastic blood involvement in MF/SS are discussed below.

Sézary cell quantification is one potential means of monitoring blood tumor burden in a clinical trials setting. B_0 has long been defined as ≤ 5% Sézary cells[1,5] and there is precedence for defining B_2 as more than 20% Sézary cells since the latter both correlates with prognosis (although not independent of skin stage)[22] and is relatively specific for MF/SS (all 71 control subjects in one study having had < 20% Sézary cells[23]). Since B_2 is currently defined as more than 1,000 Sézary cells/μL,[1] one could also use an absolute number versus percentage of Sézary cells to define B_0. Vonderheid et al[24] reported that similar survival results were seen with B_0 defined as the absence of a clone and either fewer than 20% Sézary cells or fewer than 250 Sézary cells/μL. Although Sézary cell counts are subject to considerable inter-observer variability, this hurdle could be surmounted in a clinical trial by having blood smears prepared in a standardized fashion at the study sites and sent for interpretation to an experienced pathologist at a central site. However, the cerebriform nuclear morphology that characterizes Sézary cells is not entirely specific for neoplastic T cells[13] and the number of neoplastic cells determined by Sézary cell count is often underestimated compared to flow cytometry.[25]

Conversely, flow cytometry of T-cell subsets in the blood provides a more objective, quantifiable, and reproducible means of identifying and tracking blood involvement in patients with MF/SS. The $CD4^+CD7^-$ and $CD4^+CD26^-$ subsets are most commonly used to designate the neoplastic population in MF/SS,[25-28] and the percentage of each subset currently may be used to define B_2 blood involvement.[1] However, the loss of these markers on normal T lymphocytes can occur with aging (CD7)[29,30] or with antigenic stimulation (CD7 and CD26).[27,28,31,32] In addition, clonal neoplastic T cells may be present in different populations of $CD4^+$ cells[33] and/or the population of $CD4^+$ cells with loss of expression of CD7 or CD26 may not be the dominant decrease in clone.[27,34] This makes these markers, particularly CD7,[35] less applicable for general use in clinical studies. Also, because a small proportion of normal T cells express the $CD4^+CD7^-$ or $CD4^+CD26^-$ phenotype, a decrease in these subsets in the blood may or may not indicate clearance of neoplastic cells.

Barring these limitations in specificity, utilization of the absolute number of abnormal lymphocytes by flow cytometric analysis in clinical trials to define B_2 would be in line with the current use of absolute

Table 9. Response in Blood*

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/μL[36] or Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to $\geq B_1$ in those with CR

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*As determined by absolute numbers of neoplastic cells/μL.
†If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
‡There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.
§Whichever occurs first.

number versus percentage of Sézary cells to define B_2 and would be congruent with the tracking of the absolute number of neoplastic cells in the blood in T-cell leukemias.[36] CD26 is lost on CD4+ cells in more than 90% of patients with SS and its loss correlates with morphologically identifiable tumor cells in the blood (96% sensitivity, 98% specificity).[27] Moreover, absolute counts of $CD4^+CD26^-$ cells have prognostic significance.[24]

Based on the above, at the current time, the absolute number of $CD4^+CD26^-$ cells determined by flow cytometry is the most reasonable, quantifiable measure of potential blood involvement in MF/SS for clinical trials. In CD26+ patients, $CD4^+CD7^-$ T cells would be an alternate population to monitor. Data suggest that a normal value for $CD4^+CD26^-$ or $CD4^+CD7^-$ cells by flow cytometry is lower than 15%.[27,29,30,32,37] Based on an upper limit of normal value of 1,600/μL for CD4 cells in the blood, an absolute count of lower than 250/μL $CD4^+/CD26^-$ or $CD4^+CD7^-$ cells would appear to be a normal value for these CD4 subsets and could also be used to define the absence of or normalization of blood involvement (B_0). Alternately, an absolute Sézary cell count is an optional method when good quality smears are interpreted by a single qualified reader with lower than 250/μL[24] and higher than 1,000/μL of Sézary cells[1] being reasonable determinants of B_0 and B_2.

A future method of tracking blood involvement in MF/SS may include either measuring the altered expression levels of T-cell antigens or the expression level of genes (mRNA) that are preferentially expressed by neoplastic T cells compared to normal cells, or the percentage of the malignant T-cell clone.[37]

The recommendation for definition of response in blood is given in Table 9.

GLOBAL RESPONSE SCORE: DEFINITION

In clinical trials of MF/SS, there has been no uniformity in the definition of global response (GR), an important assessment affecting overall prognosis.[19,38] We present in Table 10 the details of a consensus GR score for MF/SS. Each component of the TNMB staging (ie, skin, nodes, viscera, and blood) has been given its own definition of response (Tables 6 to 9) and these definitions are incorporated in and used to define the GR score. One important qualifier to the GR score in MF/SS should be noted: due to the primacy of the response in the skin in MF/SS, no patient with a global OR should have less than a PR in the skin.

DEFINITION OF END POINTS

A prolonged OR and progression-free survival are meaningful primary end points for all patients with MF and SS. However, the percentage of patients who achieve this OR (response rate), the time to response, the duration of response, and how it affects the patient's prognosis put the significance of the response assessment in perspective. There has previously been no uniformity in the definition of CR, PR, stable disease, or PD for MF/SS or in the

Table 10. Global Response Score

Global Score*	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.
*It is recommended that not only the proportion of patients who achieve a response or an unfavorable outcome be calculated but a life table account for the length of the interval during which each patient is under observation also be generated.

important time points that define duration of response, time to relapse, and other end points. The net result has been, in some instances, overestimation of the duration of response and in many cases, inability to directly compare study results. Table 11 details the consensus recommendations for the definition of end points in clinical trials of MF/SS, end points which attempt to be in accord with the revised response criteria for malignant lymphoma[19] after taking into account the unique differences of MF/SS from other NHLs.

SUBJECTIVE OR QUALITY OF LIFE ASSESSMENT

Patients with MF/SS often suffer tremendously from symptoms related to their disease (eg, pain, pruritus, fatigue, sleep disturbance), the social stigmata of having obvious unsightly skin lesions, the psychological/emotional problems of living with a chronic and potentially lethal disease, and often financial hardshipsrelated to therapy. Therefore, it is important that quality of life assessments

Table 11. End Points for Clinical Trials of MF/SS

End Point	Patients	Definition	Comments
ORR	CR and PR only	Proportion of patients with CR and PR	All changes in tumor measurements should be confirmed by repeat assessment no less than 4 weeks after criteria for response is first met; in NRCT, OR signifies a degree of biologic tumor activity of the investigational agent, the clinical significance which may be suggested by its magnitude, duration and CR rate; the potential for documentation of palliative effect in NRCTs increases if a historical control of patients with similar relevant prognostic variables is utilized; if feasible, confirmation of clinical benefit is always best done through a RCT
Time to response	CR and PR only	Date of initiation of treatment to date when criteria for response (PR or CR) first met	See above
Response duration	CR and PR only	Date when criteria for response (CR or PR) first met until date response first lost; date of loss of response = date when first meets criteria for PD or relapse (Tables 5-8)	Responders should have assessments at regular intervals, generally monthly, to avoid undocumented and potentially incorrect recording of persistence of response
TTR, also FFR and/or duration of complete response	CR only	Date when criteria for CR first met until time of loss of CR (relapse/recurrence) or death (as a result of MF/SS or acute toxicity of treatment)	Although a patient with a CR who no longer maintains complete clearing would no longer be disease free, he/she would remain a responder until date PR criteria is first lost
DFS	CR only	Date when criteria for CR first met until time of relapse/recurrence or death from any cause*	DFS is useful in the setting of adjuvant therapy utilized after a definitive treatment leading to CR where survival is predicted to be prolonged; 3- and 5-year DFS are of particular relevance
Duration stable disease	All patients	Date of initiation of treatment to first date meets criteria for PD	
TTP	All patients	Date of initiation of treatment to first date meets criteria for PD or death as a result of MF/SS	In TTP, death from causes other than MF/SS are censored either at the time of death or at an earlier assessment and represent a random pattern of loss from the study
PFS	All patients	Date of initiation of treatment to first date meets criteria for PD or death as a result of any cause	PFS is particularly useful as a primary end point in MF/SS
TTF and FFTF	All patients	Date of initiation of treatment until abandonment of therapy or the addition of another MF/SS specific therapy	Abandonment of therapy in TTF/FFTF does not apply to the conclusion of a standard regimen of a given therapy or discontinuation of therapy in cases of CR; causes of abandonment of therapy may include inadequate response to therapy, intolerable side effects or toxicity, disease progression, and patient withdrawal for whatever reason; TTF is particularly difficult to use in reporting retrospective results of treatments utilized to treat MF/SS in a clinical practice setting as it is common practice to add various skin-directed therapies to systemic agents to augment response
Overall survival	All patients	Date of initiation of therapy to date of death from any cause	Evaluation of survival is not optimal in clinical trials of patients with MF/SS except in those cases with late stage disease who have failed standard therapies and have a low performance score and in whom the duration of the planned trial is long enough to assess the predicted survival; in the vast majority of MF/SS patients in clinical trials, expected survival is far longer than the course of the study and the potential exists for survival to be impacted by treatment(s) given after study trial conclusion

Abbreviations: ORR, objective response rate; CR, complete response; PR, partial response; NRCT, nonrandomized clinical trials; RCT, randomized clinical trials; TTR, time to relapse; FFR, freedom from relapse; TTF, time to treatment failure; FFTF, freedom from treatment failure; DFS, disease-free survival; MF, mycosis fungoides; SS, Sézary syndrome; RFS, relapse-free survival; PD, progressive disease.

*Where death defines the end of DFS, investigators should specify whether secondary to original lymphoma, other cancer, adverse event related to therapy, or other cause.

be included in trials of MF/SS. Both the skin disease-specific Skindex-29 and the Functional Assessment of Cancer Therapy in General (FACT-G), measure patient well being. Despite neither having any specificity for MF/SS, both have been shown to be valid, reproducible, and sensitive to change, and can be completed in 5 and 10 minutes, respectively.[39] The presence of pruritus may be captured by the Skindex-29[40]or the Skindex-16[41] and quantification of severity by a visual analog scale.[10] However, to adequately assess improvement in pruritus as related to a specific treatment, one needs to determine what constitutes significant pruritus at baseline, what degree of improvement is necessary to determine whether the change is significant, and elimination of other factors that independently could affect pruritus. General terms such as pruritus relief, which imply, but do not necessarily mean, obliteration of pruritus should be avoided. All comparative pruritus measurements should be done when other treatments that can affect pruritus, such as antihistamines, are either at a stable dose or have been discontinued. No claim of absence or resolution of pruritus should be made if the measurement is taken while the patient remains on antipruritic agents. In addition, any change in pruritus should be correlated to efficacy of the study treatment so that the result can be put into perspective.

CONCLUSION

These consensus recommendations for standardization of definition of response in skin, nodes, blood and viscera, GR score, and end points in MF/SS should now allow for collation of data from different clinical trials. Given the importance of skin response in MF/SS, both skin and global response should be reported in clinical trials. This ensures that the response in the skin, which independently affects prognosis and quality of life, is not lost within the global score. It is the hope that this standardization will hasten the communication and collaboration necessary to find new effective treatments for MF and SS.

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