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Sézary syndrome: Immunopathogenesis, literature review of therapeutic options, and recommendations for therapy by the United States Cutaneous Lymphoma Consortium (USCLC)

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Sézary syndrome (SS) has a poor prognosis and few guidelines for optimizing therapy. The US Cutaneous Lymphoma Consortium, to improve clinical care of patients with SS and encourage controlled clinical trials of promising treatments, undertook a review of the published literature on therapeutic options for SS. An overview of the immunopathogenesis and standardized review of potential current treatment options for SS including metabolism, mechanism of action, overall efficacy in mycosis fungoides and SS, and common or concerning adverse effects is first discussed. The specific efficacy of each treatment for SS, both as monotherapy and combination therapy, is then reported using standardized criteria for both SS and response to therapy with the type of study defined by a modification of the US Preventive Services guidelines for evidence-based medicine. Finally, guidelines for the treatment of SS and suggestions for adjuvant treatment are noted. (J Am Acad Dermatol 2011;64:352-404.)

Key word: Sézary syndrome.

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Abbreviations used:

APL:	acute promyelocytic leukemia
ATG:	antithymocyte globulin
ATRA:	all-*trans*-retinoic acid
BIW:	twice a week
CCR4:	chemokine receptor 4
CDA:	chlorodeoxyadenosine
CLL:	chronic lymphocytic leukemia
CR:	complete response
CTCL:	cutaneous T-cell lymphoma
DC:	dendritic cell
d:	day
DCF:	deoxycoformycin
dCyk:	deoxycytidine kinase
ECP:	extracorporeal photopheresis
E-MF:	erythrodermic mycosis fungoides
EORTC:	European Organization for the Research and Treatment of Cancer
FDA:	Food and Drug Administration
GI:	gastrointestinal
Gy:	gray
HDAC:	histone deacetylase
HSCT:	hematopoietic stem cell transplantation
IC_{50}:	half maximal inhibitory concentration
IFN:	interferon
IFN-α:	interferon alfa
IFN-γ:	interferon gamma
IL:	interleukin
ISCL:	International Society for Cutaneous Lymphomas
IV:	intravenous
mAb:	monoclonal antibody
MDR:	mean duration response
MF:	mycosis fungoides
MRD:	median response duration
MTX:	methotrexate
MU:	million units
NA:	not applicable
NBUVB:	narrowband ultraviolet B
NCCN:	National Comprehensive Cancer Network
NCI:	National Cancer Institute
NK:	natural killer
OR:	objective response
PB:	peripheral blood
PK:	pharmacokinetics
PNP:	purine nucleoside phosphorylase
PR:	partial response
PUVA:	psoralen plus ultraviolet A
qd:	once daily
QLQ:	quality of life questionnaire
RA:	retinoic acid
RAR:	retinoic acid receptor
RR:	response rate
RXR:	retinoid $\times$ receptor
SC:	Sézary cell
SDF:	stromal cell-derived factor
SQ:	subcutaneous
SS:	Sézary syndrome
T_4:	erythrodermic skin stage in MF or SS
TARC:	thymus and activation- regulated chemokine
TCR:	T-cell receptor
TGF:	transforming growth factor
Th:	T helper
tiw:	3 times per week
TNF:	tumor necrosis factor
Tregs:	regulatory T-cells
TSEBT:	total skin electron beam therapy
USCLC:	US Cutaneous Lymphoma Consortium
UV:	ultraviolet
VAS:	visual analog scale
WBC:	white blood cell

DIAGNOSIS

The origin of the term "Sézary syndrome" (SS) dates back to a series of reports from 1938 to 1949 in which Sézary[1,2] described patients who presented with erythroderma and very large abnormal cells (cellules monstreuses) in the blood that he ascribed to a new malignant cutaneous reticulosis, different but related to, mycosis fungoides (MF). Since then, there has been substantial disagreement regarding the distinction between erythrodermic MF (E-MF), which may evolve slowly through patch/plaque disease and have various levels of blood involvement, and SS, which usually presents with erythroderma and significant blood involvement, and whether these are variants of the same disease.[3] Erythroderma was given a more precise definition by the International Society for Cutaneous Lymphomas (ISCL) in 2007 as erythema covering at least 80% body surface area.[4] A standardized definition of neoplastic lymphocytes in the blood and how to quantify them has been more difficult.

A method of quantifying the blood tumor burden in MF and SS was initially published in 1979 by noting the percentage of "atypical" peripheral lymphocytes with hyperconvoluted or cerebriform nuclei, now known as "Sézary cells, on a peripheral buffy coat smear."[5,6] Despite attempts over the years to provide objective definitions for these morphologically defined neoplastic lymphocytes,[7] the Sézary cell (SC) preparation remains today a subjective test with high potential for interobserver variability. Moreover, such cells in the blood are not specific for MF or SS but may be seen in healthy individuals[8] and in those with benign skin conditions.[9] Flow cytometry has introduced a more objective measure of atypical lymphocytes in MF and SS but relies on ascribing deletion of certain cell surface markers, primarily CD7[10-12] and CD26[13,14] to

CAPSULE SUMMARY

- A review of the published literature on potential treatments of Sézary syndrome (SS) has merit for clinical practice and future clinical research.

- Efficacy of treatments for SS, both monotherapy and combination therapy, is presented here in a standardized fashion using defined criteria for both the definition of SS and objective response.

- The type of study performed is reported based on evidence-based guidelines.

- Suggested guidelines for therapy of SS, including adjuvant agents, are given.

lymphomatous involvement. However, the blood of patients with benign inflammatory dermatoses may also show CD26 or CD7 deletion.[11,12,15] In addition, the correlation of the blood tumor burden by flow cytometry and by SC preparation is inexact and may offer differing results from center to center unless a single observer or a panel of experts is used to read the slides. Expansion of a clonal T-cell population assessed by polymerase chain reaction or Southern blotting to demonstrate a dominant T-cell receptor (TCR) gene rearrangement in the blood, although also not specific for lymphoma,[16-18] provides supportive evidence for significant blood involvement in the presence of an increased number of atypical lymphocytes or SCs by cytopathologic or immunophenotypic evaluation, especially if the clonal T-cell population is the same in skin and blood.

A consensus statement of the ISCL was published in 2002 to define and to draw a distinction between variants of cutaneous T-cell lymphoma (CTCL) that manifest with erythroderma.[19] Blood involvement in MF and SS was categorized into prognostically significant categories, ie: B_0 = no involvement; B_1 = low tumor burden; and B_2 = leukemic, high tumor burden. The criteria for this blood classification were further refined in the 2007 proposed revisions to the staging and classification of MF and SS prepared by the ISCL and the European Organization for the Research and Treatment of Cancer (EORTC).[4] The definition of B_2 was defined as evidence of a dominant T-cell clone by polymerase chain reaction or Southern blot plus one or more of the following findings of: (1) an absolute SC count of 1000 cells/mm^3 or higher; (2) expanded CD3$^+$ or CD4$^+$ cells with a CD4/CD8 ratio of 10 or higher; and (3) expanded CD4$^+$ T cells with abnormal immunophenotype including loss of CD7 ($\geq$ 40%) or CD26 ($\geq$ 30%). Furthermore, SS was defined as patients with both erythroderma and B_2 blood involvement and as such, would now be staged as IVA disease using the new 2007 staging revisions.[4]

IMMUNOPATHOGENESIS

As many therapies for SS, such as interferons, produce at least a portion of their clinical benefit through modification of the host immune response, a rigorous understanding of the disordered immune

response associated with SS is useful for the development of a sound therapeutic approach to this malignancy. SS is associated with significant immune abnormalities characterized by dysregulation of both cellular and humoral immunity.[20] The vast majority of cases are associated with the proliferation of a malignant population of CD4^{+} T cells that exhibit high expression of the chemokine receptor 4 (CCR4) and typically coexpression of cutaneous lymphocyte antigen.[21] Another identifying feature is the typical absence of expression of CD26 or CD7 or loss of both markers.[14,22]

A progressive impairment of cellular immunity is quite typical of advancing SS. Expansion of the malignant T-cell population appears to correlate with the progressive decline in normal cell-mediated immunity.[20,23] Wysocka et al[23] have demonstrated a direct relationship between the magnitude of the circulating burden of malignant T cells and abnormalities in multiple arms of the cellular immune response. Functions of natural killer (NK) cells, including cellular cytotoxicity and production of interferon (IFN)-γ, become increasingly impaired as circulating tumor burden increases. An inverse correlation exists between circulating tumor burden and activation status of both NK cells and CD8^{+} T cells with a diminishing number of these cells expressing the activation markers CD69 and CD25, and decreased expression of intracellular IFN-γ.[20,24] Because these cells are thought to be critical for direct antitumor responses, presumably a decline in their functions can lead to further acceleration of growth of the malignant population.[25] Another consequence of the decline in cytotoxic T-cell and NK cell functions is impaired activity against opportunistic infectious pathogens. A noticeable increase in severity of herpes viral infections in advanced SS and cases of progressive multifocal leukoencephalopathy as a result of polyomavirus[26] have been reported among patients with SS who have never been treated with chemotherapeutics or other immune-suppressing agents. Defective neutrophil function as a result of the abnormal cytokine milieu may also account for enhanced severity of bacterial infections and, perhaps, for the increase in skin colonization with *Staphylococcus aureus*. It is also possible that frequent colonization with *Staphylococcus* may be a result of impaired production of skin cathelicidin in a manner similar to that observed among patients with atopic dermatitis.[27]

The number of peripheral blood dendritic cells (DCs) and the functions of these cells also declines significantly in concert with an increasing peripheral blood tumor burden.[23] Both major populations of DCs are affected including myeloid DCs, which are known to produce interleukin (IL)-12 and IL-15, and plasmacytoid DCs, which produce IFN-α. Consequently, production of DC-dependent cytokines, including IFN-α, IL-12, and IL-15, all critical for normal antitumor and antiviral immunity, becomes progressively impaired with an increasing blood tumor burden. Direct examination of individual DCs by flow cytometry has demonstrated decreased intracellular concentrations of IL-12 within the cells obtained from patients with SS in comparison with DCs derived from the peripheral blood of age- and sex-matched healthy volunteers.[23] Thus, DC cytokine production appears to be abnormal on an individual cell basis and an overall decline in numbers of circulating DCs does not fully account for the entirety of the DC defects observed.

Emerging evidence suggests that soluble factors produced by the malignant population likely play an important role in the observed abnormalities of cellular immunity. In the majority of cases, the malignant population exhibits a T-helper (Th) 2 cell phenotype with the production of IL-4, IL-10, and in some cases IL-5.[28,29] Moreover, gene expression profiles of isolated SCs have demonstrated high expression of the Th2 transcription factor GATA-3.[30] Both IL-4 and IL-10 can exert effects to blunt NK cell and CD8^{+} T-cell functions and suppress Th1 cell immunity. Inhibition of IL-12 production from myeloid DCs and IFN-γ by NK cells by IL-10 likely also plays an important role in the decline of cellular immunity among patients with SS. Excess IL-10 production may also impede the normal differentiation of DCs.

Impaired expression of CD40 ligand on the malignant T cells, observed by French et al,[31] is another factor that may impede differentiation of DCs. The normal up-regulation of CD40 ligand during T-cell activation and its interaction with the constitutively expressed CD40 on antigen-presenting cells is crucial for optimal activation of the latter cell types. Without this interaction, there is marked impairment of activation of DCs with depressed production of IL-12. Thus, expansion of the circulating burden of malignant T cells leads to a larger population of T cells that are incapable of activating DCs during an immune response as the body is populated with an increasing number of helper T cells that are incapable of expressing CD40 ligand at the cell surface. French et al[31] has also demonstrated that provision of an appropriate stimulus for CD40 by using soluble recombinant CD40 ligand in vitro can provide the necessary signal for activation of DCs from patients with SS and the resultant reconstitution of IL-12 production. The implications of such an approach for therapy are quite significant.

Increased numbers of regulatory T cells (Tregs) have also been implicated in the immune deficiency

accompanying SS.[32,33] Several groups have reported that the malignant CD4$^+$ T cells can behave, in some cases, like Tregs in that they express Foxp3 and may produce increased levels of IL-10 and transforming growth factor (TGF)-beta. Both of these cytokines can exert profound depressive effects on DCs, NK cells, and CD8$^+$ T cells.

Loss of the normal T-cell repertoire may also impair the ability of patients with SS to respond to a diversity of antigens.[34] Yawalkar et al,[34] using beta variable complementarity-determining region 3 spectratyping, demonstrated that a loss of the normal repertoire can be observed in cases of early CTCL but is typically quite profound among patients with SS. The loss of the normal T-cell repertoire could potentially complicate the already compromised immune response against microbial pathogens. Importantly, induction of clinical remission in SS with immune therapies has been associated with recovery of T-cell diversity.[35]

A peculiar feature of SS is the less frequent occurrence of epidermotropism in comparison with early MF. Although the basis for this observation has not been clearly determined, it may be related to alterations in chemokine gradients that occur with the leukemic phase of CTCL. The skin-derived chemokines of thymus and activation-regulated chemokine (TARC) and stromal cell-derived factor (SDF)-1, ligands for CCR4 and fusin (CXCR4), respectively, are produced at increased levels by the skin of patients with CTCL. This would be expected to lead to recruitment of malignant T cells that highly express CCR4 and fusin (CXCR4).[36] Nevertheless, the reportedly high serum levels of TARC and SDF-1 that occur in SS could compete with cutaneous gradients of chemokines and, thus, could alter the migratory patterns of the malignant cells away from the epidermis. Once the malignant cells arrive within the cutaneous environment, a relevant issue in regard to proliferation of malignant T cells within the skin is the observation by Yamanaka et al[37] that skin-derived IL-7 may be an important stimulus for perpetuation of growth of the abnormal CD4$^+$ population.

Importantly, most, if not all of the described immune abnormalities associated with SS have been observed to normalize after clinical remission induced by immune modulatory therapies including photopheresis, interferons, and systemic retinoids.[38] On clearance of the malignant cells, repopulation of the peripheral blood with NK cells, CD8$^+$ T cells, and DCs that all function normally is quite characteristic.[20,39] Although chemotherapeutic regimens may induce transient remission, their immunosuppressive effects impede immune reconstitution. One

important implication of these observations is that the malignant CD4$^+$ T cells are likely responsible for the numerous abnormalities of cellular immunity. If these cells can be cleared using an immune-potentiating regimen, immune reconstitution is possible. Moreover, the ability to respond to microbial pathogens will likely improve as well.

THERAPEUTIC OPTIONS
Overview

The overall prognosis of patients with SS is poor with few lasting remissions and responses that may not address the disabling pruritus that so affects quality of life. The most relevant information available today on the survival of patients with SS comes from patients seen at Stanford University Medical Center between 1958 and 1999 with a histologic diagnosis of MF/SS and SC counts of either more than 1000/mm^3 or more than 20% of peripheral blood lymphocytes, 80% of whom also had erythrodermic skin disease.[39] Median survival was 2.9 years in this subgroup of primarily patients with SS according to current criteria. Much has changed since 1999 including the creation of additional objective criteria for the definition of SS,[4] the regular use of immuno-modulatory agents in SS,[40] and the availability of new chemotherapeutic drugs or monoclonal antibodies (mAb) with documented activity in SS.[41,42] There are few publications that address what effect on survival these changes have wrought.[43] There also are few data on the relative efficacy of the therapeutic options for patients with SS for a variety of reasons: (1) there is a small number of patients with SS compared with patients who have MF (5%-6% total)[44]; (2) patients with SS are commonly excluded from clinical trials of MF; (3) the majority of articles have been published before both international consensus definitions of SS and the incorporation of blood into the staging of MF and SS and, hence, the response in patients with E-MF with no or low levels of blood involvement and patients with SS have often been grouped together; (4) many studies group the efficacy results in those with "aggressive" or "late stage" or stage IIB or greater MF/SS together versus separating out the results in patients with SS separately; and (5) the definition of endpoints has often varied between studies.

Despite these limitations and because of a dire need to improve the treatment and prognosis of these patients, we have undertaken a literature review of the current therapeutic options for SS. Each therapeutic option has been evaluated in a standard format in an attempt to control for as many variables as possible and allow for a comparison of the various agents on a single plane. We have first

provided information on the mechanism of action, overall efficacy in MF/SS (to provide a point of comparison with those patients with SS), and adverse effects of each agent. We have then reported on the results for each agent used as a monotherapy (Table I) or as part of combination therapy specifically in SS (Table II), noting the definition of SS, the response criteria used, and type of study in each publication. There are no published trials in SS with an active control group and most data on efficacy are from individual patients so designated within a study of patients with MF/SS. Nonetheless, we assigned a hierarchy of research design using a modification of the US Preventive Services guidelines for evidence-based medicine[45]: level I is evidence obtained from at least one properly randomized controlled trial; level II-1 is evidence obtained from at least one well-designed controlled trial without randomization; level II-2 is evidence obtained from at least one prospective, well-designed cohort or case-control study, preferably from more than one center or research group; level II-3 is evidence obtained from at least one retrospective, well-designed cohort or case-control study, preferably from more than one center or research group; level III is evidence obtained from multiple time series with or without the intervention; and level IV includes opinions of respected authorities, based on clinical experience, descriptive studies, and case reports or reports of expert committees. The results of bone-marrow transplantation in SS are given in Table III. Guidelines for the treatment of SS proposed by the US Cutaneous Lymphoma Consortium (USCLC) are given in Table IV: these are modified from the National Comprehensive Cancer Network (NCCN) guidelines published in 2009 of which several members of the USCLC participated.[46]

IMMUNOMODULATING AGENTS
Interferon alfa

There are two forms of recombinant interferon alfa—interferon alfa-2a (Roferon) and interferon alfa-2b (Intron)—that have been studied in the treatment of MF/SS for more than 20 years although neither is specifically approved for this indication. Interferon alfa-2a and -2b differ in structure by one amino acid at position 23 and in their method of purification but bind to the same type I IFN receptor with purportedly the same biologic specific activity.[47] Subcutaneous (SQ) or intramuscular injections of interferon alfa are equivalent with an elimination half-life of 2 to 3 hours for interferon alfa-2b and 3 to 8 hours for interferon alfa-2a.[48] Interferon alfa-2a is no longer available in the United States but has been supplanted by its pegylated form (Pegasys). There

is also a pegylated form of interferon alfa-2b (PegIntron) although neither of the pegylated forms has published efficacy reports in clinical trials of MF or SS. The pegylated forms differ quite a bit in their size and structure with pegylated interferon alfa-2a being a much larger molecule (40 vs 12 kd) and having a longer elimination half-life (80 [50-140] vs 40 [22-60] hours) than pegylated interferon alfa-2b, which acts primarily as a prodrug with slow interferon release.[48] There is also another Food and Drug Administration (FDA)-approved interferon alfa, interferon alfacon-1 (Infergen), which is a recombinant, nonnaturally occurring type-1 IFN derived from several natural IFN-α subtypes and differing from interferon alfa-2b at 20/166 amino acids and with identity of 30% or more of amino acid positions of interferon beta.[49] It is FDA approved for the treatment of hepatitis C and, to date, there have been no published clinical trials using it in CTCL.

Interferons as a class have cytotoxic, antiproliferative, and antiviral properties. Interferon alfa increases class I molecules on lymphocytes and has a variable effect on NK activity and antibody production by B cells.[50-52] Importantly as pertains to CTCL, interferon alfa inhibits production of IL-4 and IL-5 by normal T cells and SCs, thus suppressing the Th2 cytokine secretion pattern.[53,54] Development of resistance to interferon alfa has been observed[55-57] and has been hypothesized to be related to the presence of neutralizing antibodies (dose/duration/route related),[47,58] down-regulation of IFN receptors,[59] or more recently, a lack of STAT1 expression.[60]

Interferon alfa has efficacy across all stages of MF and SS.[47] Papa et al[61] showed that 80% of patients with patch/plaque disease and 70% of patients with stage III/IV disease (including SS) treated with 18 million units (MU) interferon alfa-2a daily for 3 months and then 3 times per week (tiw) had an objective response (OR) (OR = complete response [CR] [100% clearing] plus partial response [PR] [at least 50% clearing]). This was very similar to that of the Duke University Medical Center and Northwestern University Medical Center study with 73% and 60% OR in those with similar stages of disease[55] but on 3 to 18 MU daily of interferon alfa-2a. The maximally tolerated dose of interferon alfa is 9 to 18 MU daily with most patients being treated in practice with 3 to 6 MU tiw to daily. However, there may be an advantage to higher doses of interferon alfa especially with waning response to low-dose interferon.[55,62,63] Reports of patients with SS treated with interferon alfa are limited. Several studies failed to give criteria for the diagnosis of SS but reported responses. Dallot et al[64] reported improvement in 3 of 5 patients with SS treated with 5 MU interferon

Table I. Monotherapies in Sézary syndrome

Treatment	Author	No. of SS/total patients in study	Definition SS	Dose	Duration of response	Definition response	Response rate	Type of study
2-Chlorodeoxyadenosine		**Level of evidence: II-2**						
2-Chlorodeoxyadenosine	Saven et al[191]	3/9	T_4 B_1	0.05-0.15 mg/kg × 7 d q 4 wk	5 mo	SNM	OR 33% (1/3); CR none	Prospective cohort study (1 site)
2-Chlorodeoxyadenosine	Bouwhuis et al[193]	6/6	T_4 + >1000/mm^3 PB SC	5 mg/m^2 intermittent infusion q 6 wk	9+ mo	SNB	OR 50% (3/6); CR 17% (1/6)	Retrospective cohort study (1 site)
Alemtuzumab		**Level of evidence: II-2**						
Alemtuzumab	Kennedy et al[269]	2/6	T_4 + PB SC	30 mg IV tiw × 12 wk	<3 mo	SNM	OR 100% (2/2); CR none	Phase II study (1 site)
Alemtuzumab	Alinari et al[273]	3/5	T_4 + ISCL B_2 criteria	30 mg SQ tiw × 5-9 wk	MRD 3 mo (3 - 17+)	SNB	OR 100% (3/3); CR 100% (3/3)	Compassionate plea case series (2 sites)
Alemtuzumab	Gautschi et al[274]	1/1	T_4 + >1000 CD4$^+$/CD7$^-$ cells/mm^3 + WBC >32,000	30 mg IV tiw × 10 wk	12+ mo	SNB	OR 100% (1/1); CR 100% (1/1)	Case report (1 site)
Alemtuzumab	Querfeld et al[275]	17/19	T_4 + ISCL B_2 definition	3 mg on d 1, 10 mg on d 3, 30 mg on d 5 then 30 mg tiw × 12 wk	6 mo (0 - 39+)	SNMB	OR at least 82% (SS patients not separated out)	Phase II trial and retrospective cohort study (1 site)
Bexarotene		**Level of evidence: II-2**						
Bexarotene	Duvic et al[110]	17/94	T_4 + ≥10% PB SC	300 mg/m^2/d	UNK	SNM	OR 24% (4/17); CR none	Phase II-III study (26 sites)
Bexarotene	Abbott et al[111]	9/28	T_4 + ISCL B_2 criteria	150-300 mg/m^2 initially then 300 mg/m^2/d	MRD 9 mo	SNB	OR 78% (7/9); CR 22% (2/9)	Retrospective cohort study (1 site)
Bexarotene	Bagot[112]	1/1	T_4 + >20% PB SC	300 mg/m^2/d	MRD 17 mo	SB	OR 100% (1/1); CR 100% (1/1)	Case report (1 site)
Bexarotene	Bouwhuis et al[113]	2/6	T_4 + >1000 PB SC/mm^3 + clone	300-650 mg/d	NA	SNMB	OR none	Case series (1 site)
Bexarotene	Ruiz-de-Casas et al[114]	1/1	T_4 + >20% PB SC	300 mg/m^2/d	NA	S	OR none	Case report (1 site)

Chlorambucil		Level of evidence: II-3						
Chlorambucil	Coors and von den Driesch[97]	11/13	T_4 + >10% PB SC	Chlorambucil 10-12 mg/d + fluocortolone 75/50/25 mg × 3 d q 2-6 wk pulse treatment	~16.5 mo	S	OR 100% (11/11); CR 45% (5/11)	Retrospective cohort study (1 site)
Chlorambucil	Hamminga et al[223]	6/8	T_4 + ≥10% PB SC + keratoderma + lymphadenopathy	Chlorambucil 2-6 mg/d, prednisone 5-20 mg/d	NG	SNB	OR 100% (6/6); CR none	Case series (1 site)
Chlorambucil	Winkelmann et al[224]	26/26	T_4 + >15% or >1000/mm³ PB SC	~4 mg (2-6)/d chlorambucil + 20 mg/d prednisone, maintenance chlorambucil 2-4 mg + prednisone 5-10 mg/d	7/19 CR documented >1 y	SB	OR 88% (23/26); CR 35% (9/26)	Retrospective cohort study (1 site)
Denileukin diftitox		Level of evidence: II-3						
Denileukin diftitox	Foss et al[145]	8/15	T_4 with circulating $CD4^+CD7^-$ cells	9 or 18 μg/kg + prednisone 20 mg or Decadron 8 mg/d × 5 d q 3 wk	3+ mo	SNB	OR 50% (4/8); CR none	Retrospective cohort study (2 sites)
Denileukin diftitox	Chin and Foss[146]	6/37	T_4 + >1000/mm³ PB SC	4-18 μg/kg qd × 5 days first cycle + Decadron 8 mg then 18-27 μg/kg qd × 5 + Decadron 8 mg q 3 wk	Median 30 wk	SNB	OR 50% (3/6); CR none	Retrospective cohort study (1 site)
Deoxycoformycin		Level of evidence: II-2						
Deoxycoformycin	Ho et al[200]	21/43	T_4, adenopathy, and leukemic blood picture	4 mg/m² × 3 d q wk × 3 then qowk × 6 wk then monthly	DFS 24.9 wk	SBNM	OR 33% (7/21); CR 5% (1/21)	Phase II study (7 sites)

Continued

Table I. Cont'd

Treatment	Author	No. of SS/total patients in study	Definition SS	Dose	Duration of response	Definition response	Response rate	Type of study
Deoxycoformycin	Mercieca et al[201]	16/45	T_4 + PB SC	4 mg/m^2 weekly × 4 wk, then qowk	2 CRs 3+ and 7+ y; PR = 3-12 mo	SBNM with OR at least 3 mo duration	OR 63% (10/16); CR 19% (3/16)	Retrospective cohort study (1 site)
ECP		**Level of evidence: II-2**						
ECP	Dippel et al[84]	2/10	T_4 + >5% PB SC	ECP 2 d q 2-4 wk	Average 16 mo of ECP	SNB	OR none	Retrospective cohort study (1 site)
ECP	Vonderheid et al[90]	4/6*	T_4 + >15% PB SC + either clone, abn by flow or chromosomal abn	ECP 2 d q 4 wk × ≥ 12 wk	NA	SBN	OR none	Retrospective cohort study (1 site)
ECP	Bouwhuis et al[151]	55/55	T_4 + PB SC count ≥ 1000 cells/mm^3	ECP 2 d q 4 wk	UNK	SNB	OR 18% (10/55); CR none	Retrospective cohort study (1 site)
ECP	Zic et al[153]	1/20*	T_4 + >5% atypical lymphocytes	ECP 2 consecutive d q 4 wk × at least 6 mo + topical steroids	53+ mo	S	OR 100% (1/1); CR 100% (1/1)	Retrospective cohort study (1 site)
ECP	Crovetti et al[154]	9/33*	T_4 + PB SC + pruritus, lymphadenopathy, and BM SC	ECP 2 consecutive d either q 4 wk × 6 mo or q 2 wk × 3 mo then q 4 wk × 3 mo	UNK	SN	OR 67% (6/9); CR 33% (3/9)	Retrospective cohort study (1 site)
ECP	Arulogun et al[155]	3/13*	T_4 + 2/3 of >5% PB SC, CD4/CD8 ≥ 10 or PB clone	ECP biw × 1 wk, q wk × 6 wk then q mo	UNK	SNB	OR 33% (1/3); CR none	Retrospective cohort study (1 site)
ECP	Stevens et al[156]	15/17	T_4 + >5% PB SC + either PB clone or ≥ 80% CD4$^+$/CD7$^-$	ECP 2 d q 2 wk × 8 wk then q 4 wk	5/6 >5 y on maintenance treatment	SNMB	OR 40% (6/15); CR 40% (6/15)	Prospective cohort study (1 site)
ECP	Russell-Jones et al[157]	19/19	T_4 + TCRGR clone	ECP (no further specifics given) ×1 y	UNK	S	≥90% Clearing in 3/19; additional PR unclear	Retrospective cohort study (1 site)

ECP	de Misa et al[158]	10/10	T_4 + >5% PB SC + PB clone	ECP 2 d q 4 wk × 1 y	UNK	S	1/10 CR; PR unclear	Retrospective cohort study (3 sites)
Etretinate			**Level of evidence: II-2**					
Etretinate	Molin et al[129]	1/24	NG	0.2-2 mg/kg/d	NG	S	OR none	Prospective cohort study (8 sites)
Etretinate	Claudy et al[132]	1/6	T_4 + >1000 PB SC	0.8-1 mg/kg/d	8+ mo	SNB	OR 100% (1/1); CR none	Case series (one site)
Fludarabine			**Level of evidence: II-2**					
Fludarabine	Quaglino et al[181]	17/44	T_4 + >1000/mm³ PB SC	25 mg/m² × 5 d q 28 d	Unable to determine	SNB	OR 35% (6/17); CR 18% (3/17)	Phase II study (1 site)
Fludarabine	Nikko et al[182]	1/1	T_4 + increased WBC and PB SC	25 mg/m² × 5 d q 28 d	14 mo	SNB	OR 100% (1/1); CR 100% (1/1)	Case report (1 site)
Gemcitabine			**Level of evidence: II-2**					
Gemcitabine	Duvic et al[205]	11/33	T_4 + ISCL definition B_2	On d 1, 8, 15 at 1000 mg/m² ≥6 cycles; 3 of 8 patients treated off-study at 150 mg/m²	All patients: med duration PRs = 4.1 mo	SNB	OR 73% (8/11); CR none	Phase II study (1 site)
Interferon alfa			**Level of evidence: II-2**					
Interferon alfa-2a	Papa et al[61]	6/43 (23/43 Stage II-IV)	NG but SS separate from stage III	3->18 MU qd over 15 days to 18 MU qd then max tolerated dose tiw	All patients MRD 23.2 mo (SS not separated out)	SB	OR 33% (2/6 prior treatment had PR, UNK those no prior treatment)	Prospective cohort study (3 sites)
Interferon alfa-2a	Jumbou et al[67]	11/51 (SS +1 stage IV reported together)	T_4 + ≥5% PB SC	Mean 2.7 MU qd	All patients l CR 1.3-53 mo (SS not separate)	NG	OR 25% (3/12); CR 16.5% (2/12)	Retrospective cohort study (1 site)
Interferon gamma			**Level of evidence: II-2**					
Interferon gamma	Kaplan et al[99]	At least 2/16	T_4 + PB SC	250 μg/m²/d IM × 1 wk, then 500 μg/m²/d	3 mo	SNM	OR 50% (1/2); CR none	Phase II study (2 sites)

Continued

Table I. Cont'd

Treatment	Author	No. of SS/total patients in study	Definition SS	Dose	Duration of response	Definition response	Response rate	Type of study
Isotretinoin		**Level of evidence: II-2**						
Isotretinoin	Molin et al[129]	5/15	NG	0.2-2 mg/kg/d	NG	S	OR 20% (1/5); CR none	Prospective cohort study (8 sites)
Liposomal doxorubicin		**Level of evidence: II-2**						
Liposomal doxorubicin	Wollina et al[247]	1/34	T_4 + ISCL criteria B_2	20 mg q 4 wk 27/34, rest 30-40 mg q 2-3 wk: 2/34 also received interferon alfa	Overall MRD >12 mo; 18+ mo SS	SNBM	OR 100% (1/1); CR 100% (1/1)	Retrospective cohort study (7 sites)
Liposomal doxorubicin	Pulini et al[248]	3/19	T_4 + ISCL criteria B_2	20 mg q 4 w	Overall PFS = 19 mo	SNBM	OR 67% (2/3); CR 33% (1/3)	Phase II study (4 sites)
Liposomal doxorubicin	Quereux et al[249]	10/25 Including 5 with LCT	T_4 + ISCL criteria B_2	40 mg q 4 wk	Overall PFS 5 mo, 60% CR relapse med 358 d	SNBM	OR 60% (6/10); CR 10% (1/10)	Prospective cohort study (13 sites)
Mechlorethamine		**Level of evidence: II-2**						
Mechlorethamine	Van Scott et al[227]	6/41	T_4 + ≥20% PB SC	Regimens include IV push 0.5-3 mg qd, 1-3 mg tiw, 1-1.5 mg bid or 2 mg over slow infusion to course of 0.4 mg/kg	UNK	Change in stage	OR 67% (4/6); CR none	Prospective cohort study (1 site)
Methotrexate, high dose		**Level of evidence: II-2**						
Methotrexate	McDonald and Bertino[170]	1/11	T_4 + >5% SC and increased WBC	60-240 mg/m^2 over 24-h IV infusion with leucovorin rescue; escalating dose q 5 d; maintenance oral dose 25-50 mg/wk or 60-240 mg/m^2/wk with leucovorin rescue	35+ mo	S	OR 100% (1/1); CR 100% (1/1)	Prospective cohort study (2 sites)

Methotrexate, low dose		**Level of evidence: II-3**						
Methotrexate	Zackheim et al[167]	10/29	T_4B_2	5-125 mg/wk without leucovorin	FFTR: CR 17, 48 and 129 mo; PR 31 and 101 mo	S (unclear if N, B considered)	OR 50% (5/10); CR 30% (3/10) [OR 61%, CR 50% if definition SS is PB SC > 30%]	Retrospective cohort study (1 site)
Romidepsin		**Level of evidence: II-2**						
Romidepsin	Whittaker et al[257]	13/96	T_4 + ISCL criteria B_2	14 mg/m² as 4-h IV infusion on d 1, 8, and 15 q 28 d for up to 6 cycles	NG	S	OR 31% (4/13); CR none	Phase II study
Vorinostat		**Level of evidence: II-2**						
Vorinostat	Olsen et al[41]	30/74	T_4 + ISCL criteria B_2	400 mg oral/d	Not reached (34+ - 441+ d)	S	OR 33% (10/30); CR none	Phase IIb study (7 sites)
Vorinostat	Duvic et al[253]	11/33	T_4 + ISCL criteria B_2	400 mg qd or 300 mg bid × 3 d/wk × 4 wk, then 5 d/wk or 300 mg bid × 14 d with 7-d rest	15.1 wk	S	OR 36% (4/11); CR none	Phase II study (1 site)

abn, Abnormal; *B*, blood; *B₁*, >5% SC per ISCL/European Organization for the Research and Treatment of Cancer (EORTC) classification[4]; *B₂*, high blood tumor burden per ISCL/EORTC classification[4]; *bid*, twice a day; *BM*, bone marrow; *CR*, complete response; *DFS*, disease-free survival; *ECP*, extracorporeal photopheresis; *FFTR*, freedom from treatment failure; *IM*, intramuscularly; *ISCL*, International Society for Cutaneous Lymphomas; *IV*, intravenous; *LCT*, large cell transformation; *M*, viscera; *MRD*, median response duration; *MU*, million units; *N*, nodes; *NA*, not applicable; *NG*, not given; *OR*, objective response (CR + PR); *PB*, peripheral blood; *PR*, partial response; *q*, every; *qd*, once daily; *qowk*, every other week; *S*, skin; *SC*, Sézary cells; *SQ*, subcutaneous; *SS*, Sézary syndrome; *T₄*, erythrodermic stage (mycosis fungoides or SS); *TCRGR*, T-cell receptor gene rearrangement; *tiw*, 3 times weekly; *UNK*, unknown; *WBC*, white blood cell.

Levels of evidence[45]: I = evidence obtained from at least one properly randomized controlled trial; II-1 = evidence obtained from at least one well-designed controlled trial without randomization; II-2 = evidence obtained from at least one prospective, well-designed cohort or case-control study, preferably from more than one center or research group; II-3 = evidence obtained from at least one retrospective, well-designed cohort or case-control study, preferably from more than one center or research group; III = evidence obtained from multiple time series with or without intervention; IV = includes opinions of respected authorities, based on clinical experience, descriptive studies, and case reports or reports of expert committees.

Publications included must have described Food and Drug Administration—approved treatment, definition of SS used, dosing regimen used, and had definition of response as ≥50% clearance from baseline. In cases where definition of SS was not specifically given, extrapolation could be made from history that subjects likely met current criteria of SS.

*These publications reported only evaluable patients who completed minimum number of treatments.

Table II. Combination therapies in Sézary syndrome

Treatment	Author	No of SS/total patients in study	Definition SS	Dose	MRD	Definition response	Response rate in SS	Type of study	Level of evidence
Interferon alfa + ECP	Ferenczi et al[80]	1/1	T$_4$ + CD4/CD8 14.8	ECP 2 consecutive d q 3 wk + interferon alfa 3 MU tiw	UNK	SB	OR 100% (1/1); CR 100% (1/1)	Case report (1 site)	II-2
Interferon alfa + ECP	Haley et al[81]	1/1	T$_4$ + >1000 PBSC/μL + CD4/CD8 >16	ECP 2 consecutive d q 4 wk; interferon alfa up to 36 MU qd	48 mo	SNB	OR 100% (1/1); CR 100% (1/1)	Case report (1 site)	
Interferon alfa + ECP	Vonderheid et al[82]	5/6	T$_4$ or diffuse dermatitis + >15% PBSC	Interferon alfa-2b 3-20 MU tiw; ECP 2 consecutive d q 4 wk	UNK	SB	OR 17% (1/6); CR none	Prospective cohort study (1 site)	
Interferon alfa + ECP	Bouwhuis et al[83]	1/1	T$_4$ + CD4/CD8 4:1 + >1000 PBSC/μL + clone	Interferon alfa-2b 3 MU SQ 5×/wk + ECP monthly	>2 y; Comment that only 1 of 155 patients with SS so treated to have sustained remission	S	OR 100% (1/1); CR 100% (1/1) but B$_1$ + negative B clone	Case report (1 site)	
Interferon alfa + ECP	Dippel et al[84]	1/9	T$_4$ + >5% PBSC	Interferon alfa 3-18 MU tiw; ECP 2 consecutive d q 4 wk	NA	SNVB	OR none	Retrospective cohort study (1 site)	
Interferon alfa + ECP	Rook et al[85]	1/1	T$_4$ + 46% PBSC	Interferon alfa-2b 5 MU qod; ECP 2 consecutive d q 4 wk	>18 mo	SNB	OR 100% (1/1); CR none	Case report (1 site)	
Interferon alfa + ECP	Cohen et al[86]	1/1	T$_4$ + >1000 SC/μL + clone	Interferon alfa 2-5 MU qod; ECP 2 consecutive d q 4 wk	6+ mo	SB	CR 100% (1/1)	Case report (1 site)	
Interferon alfa + ECP	Vonderheid et al[90]	11/12	T$_4$ + >15% PBSC + either clone, abn flow or chromosomal abn	Interferon alfa + ECP 2 d q 4 wk × ≥12 wk	UNK	SBN	OR 36% (4/11); CR 9% (1/11)	Prospective cohort study (1 site)	

Treatment	Author	N	Criteria	Regimen	Duration/relapse	Code	Response	Study type	Level
Interferon alfa + ECP + PUVA + topical steroids	Booken et al[88]	12/12	T_4 + ISCL criteria B_2	Interferon alfa-2a 3-9 MU tiw; ECP 2 consecutive d q 2-4 wk, PUVA tiw, topical steroids	UNK	SBN	OR 42% (5/12); CR 8% (1/12)	Retrospective cohort study (1 site)	
Interferon alfa-2a + PUVA	Chiarion-Sileni et al[72]	2/63	T_4 + >5% PBSC	3 MU escalated to 12 MU tiw over 1 mo then continuous dosing + PUVA tiw	NA	SNB	OR none	Prospective phase II study (5 sites)	II-2
Bexarotene + interferon alfa	Ranki[91]	1/1	T_4 + >50% PBSC	Bexarotene 250 mg/m^2/d + interferon alfa (dose UNK)	5 mo	SB	OR 100% (1/1); CR none	Case report (1 site)	III
ECP + interferon alfa + BRM	Richardson et al[92]	28/28	T_4 + one or more of >1000 PBSC/μL or CD4/CD8 $\geq$10 or T-cell clone with increased lymphocyte count or chromosomal abnormality	ECP 2 consecutive d q mo $\times$ >6 mo + interferon alfa 1.5 MU 3-5$\times$/wk + bexarotene 24/28 patients $\pm$ interferon gamma 40-100 μg 3-5$\times$/wk, acitretin, GMCSF, PUVA + topical NM + topical BCNU, UVB	CR: 2 relapse 3 and 40 mo, others >36 mo; PR 4-24 mo	S	OR 89% (25/28); CR 29% (8/28)	Retrospective cohort study (1 site)	II-3
ECP + bexarotene	Tsirigotis et al[115]	2/5	T_4 + > 1000 PBSC/μL	ECP 2 consecutive d q wk $\times$ 1 mo, qowk $\times$ 1 mo then q mo + bexarotene 300 mg/m^2	3 and 5 mo	SB	OR 100% (2/2); CR none	Prospective cohort study (1 site)	II-2
ECP + bexarotene	Bouwhuis et al[113]	3/6	T_4 + >1000 SC/μL + clone	Bexarotene 300-650 mg/d + ECP	NA	SNVB	OR none	Case series (1 site)	III
ECP + interferon alfa + prednisone + bexarotene	Bagazgoitia et al[93]	1/1	T_4 + >20% PBSC	Interferon alfa 6 MU tiw + prednisone 20 mg/d + ECP monthly X 3 yrs + addition bexarotene 450 mg/d	NA	S	OR none	Case report (1 site)	III

Continued

Table II. Cont'd

Treatment	Author	No of SS/total patients in study	Definition SS	Dose	MRD	Definition response	Response rate in SS	Type of study	Level of evidence
ECP + interferon alfa, + MTX + topical NM	Vonderheid et al[90]	3/4	T_4 + >15% PBSC + either clone, abn by flow or chromosomal abn	ECP 2 d q 4 wk × ≥12 wk, other treatment regimens not specified	UNK but both went on to PD	SBN	OR 67% (2/3); CR none	Prospective cohort study (1 site)	II-2
ECP + interferon alfa + IL-2	Fritz et al[94]	1/1	T_4 + CD4/CD8 66 + 47% CD4$^+$/CD7$^-$	ECP d 1 + interferon alfa-2a 4.5 MU × 7 d then tiw × 3 wk + IL-2 18 MU IV d 1, 9 MU d 2-5 in 3 wk cycle × 6 cycles	8 mo	S	OR 100% (1/1); CR none	Case report (1 site)	III
ECP + interferon gamma + bexarotene + PUVA	Shapiro et al[100]	1/1	T_4 + >23% PBSC	Interferon gamma 4.2 MU SQ 4×/wk + monthly ECP + bexarotene 150 mg/d + PUVA biw	MRD not reached at 6 mo	SB	OR 100% (1/1); CR 100% (1/1)	Case report (1 site)	III
ECP + interferon gamma + bexarotene + PUVA	McGinnis et al[95]	1/1	CD4/CD8 48 or ≥20% PBSC	Monthly ECP + interferon gamma MU SQ 4×/wk + bexarotene 150-225 mg/d + PUVA	16+ mo	SB	OR 100% (1/1); CR 100% (1/1)	Case series (1 site)	
Interferon alfa-2b + ECP + bexarotene + PUVA	McGinnis et al[95]	2/2	T_4 + >20% PBSC	Interferon alfa-2b 1.8-2.4 MU tiw + ECP + bexarotene 75-300 mg/d + PUVA	5 mo	SN	OR 100% (2/2); CR none	Case series (1 site)	III
ECP + bexarotene + PUVA	McGinnis et al[95]	1/1	T_4 + >20% PBSC	Monthly ECP + bexarotene 150 mg/d + PUVA	≥6 mo	SB	OR 100% (1/1); CR none	Case series (1 site)	III
ECP + TSEBT + interferon gamma + bexarotene	McGinnis et al[101]	1/1	T_4 + >30% PBSC	Interferon gamma 40 μg SQ tiw added to ECP + bexarotene 150 mg/d post-TSEBT	≥3 y	SB	OR 100% (1/1); CR 100% (1/1)	Case report (1 site)	III
ECP + MTX	Vonderheid et al[90]	2/3	T_4 + >15% PBSC + either clone, abn by flow or chromosomal abn	ECP 2 d q 4 wk × ≥12 wk + MTX (dose NG)	UNK	SBN	OR 50% (1/2); CR none	Prospective cohort study (1 site)	II-2

ECP + TSEBT + chemotherapy	Zic et al[153]	1/20	T_4 + >5% atypical lymphocytes	ECP 2 consecutive d q 4 wk × at least 6 mo + TSEBT + chemotherapy (unspecified)	NA	S	OR none	Retrospective cohort study (1 site)	II-3
Interferon gamma + vorinostat + ECP	Gardner et al[102]	1/3	T_4 + 74% CD4$^+$/CD26$^-$ PB lymphocytes	Interferon gamma 100 μg SQ tiw + vorinostat 400 mg oral qd + ECP q 4 wk	14 mo	S	OR 100% (1/1); CR none	Case series (1 site)	III
TSEBT + interferon alfa + ECP ± bexarotene	Introcaso et al[96]	4/4	T_4 + CD4$^+$/CD7$^-$ ≥10%, CD4:CD8 ratio ≥ 6.2, CD4$^+$/CD26$^-$ ≥ 58%	TSEBT added to regimen of interferon alfa + ECP ± bexarotene (no specifics given)	NG	S	OR 100% (4/4); CR 100% (4/4)	Case series (2 sites)	III
Fludarabine + interferon alfa	Foss et al[79]	11/35	T_4 + PBSC	Fludarabine 25 mg/m^2 × 5 d q 28 d; interferon 5-7.5 MU SQ tiw	PFS CR = ≥ 18 mo	SNMB	OR 27% (3/11); CR 27% (3/11)	Phase II study (2 sites)	II-2
Fludarabine + Cytoxan	Scarisbrick et al[185]	8/9	T_4 + >10% PBSC + clone	Fludarabine 18 mg/m^2 d 1 and Cytoxan 250 mg/m^2 × 3 d q mo	10 mo	SNMB	OR 63% (5/8); CR 13% (1/8)	Prospective cohort study (1 site)	II-2
Chlorambucil + fluocortolone + interferon alfa	Coors and von den Driesch[97]	1/13	T_4 + >10% PBSC	Chlorambucil 10-12 mg + fluocortolone 75/50/25 mg × 3 d q 2-6 wk pulse treatment + interferon alfa (dose NG)	NG	S	OR 100% (1/1); CR 100% (1/1)	Prospective cohort study (1 site)	II-2
Chlorambucil + fluocortolone + interferon alfa + PUVA	Coors and von den Driesch[97]	1/13	T_4 + >10% PBSC	Chlorambucil 10-12 mg + fluocortolone 75/50/25 mg × 3 d q 2-6 wk pulse treatment + PUVA	NG	S	OR 100% (1/1); CR 100% (1/1)	Prospective cohort study (1 site)	II-2
Chlorambucil + fluocortolone + PUVA	Coors and von den Driesch[97]	4/13	T_4 + >10% PBSC	Chlorambucil 10-12 mg + fluocortolone 75/50/25 mg × 3 d q 2-6 wk pulse treatment + interferon alfa + PUVA	NG	S	OR 100% (3/3); CR 67% (2/3)	Prospective cohort study (1 site)	II-2

Continued

Table II. Cont'd

Treatment	Author	No of SS/total patients in study	Definition SS	Dose	MRD	Definition response	Response rate in SS	Type of study	Level of evidence
Chlorambucil + leukapheresis	McEvoy et al[225]	11/11	T₄ + >1000/µL PB SC	Chlorambucil 4 mg/d + prednisone 20 mg/d + leukopheresis 2-3×/wk	Mean time to relapse PR all patient 12 mo	SB	OR 100% (11/11); CR 18% (2/11)	Retrospective cohort study (1 site)	II-3
MTX + 5-FU	Schappell et al[172]	2/10	T₄ + >5% PBSC	MTX 60-120 mg/m² IV + leucovorin; 5-FU 20 mg/kg cycles	NG	S + ?	OR 100% (2/2 >80% clearing); CR none	Prospective cohort study (1 site)	II-2
MTX + etoposide	Hirayama et al[173]	1/1	T₄ + >13,500 CD4⁺ lymphocytes	MTX 10 mg/wk orally; etoposide 25 mg qd orally	NG	SNB	OR 100% (1/1); CR none	Case report (1 site)	III

+, Plus; +/-, with or without; *abn*, abnormal; *B*, blood; *BCNU*, bis-chloronitrosourea; *BRM*, biologic response modifier; *CR*, complete response; *ECP*, extracorporeal photopheresis; *FU*, fluorouracil; *GMCSF*, granulocyte monocyte colony-stimulating factor; *IL*, interleukin; *IV*, intravenous; *MRD*, median response duration; *MTX*, methotrexate; *MU*, million units; *N*, nodes; *NA*, not applicable; *NG*, not given; *NM*, nitrogen mustard; *OR*, objective response; *PB*, peripheral blood; *PD*, progressive disease; *PFS*, progression-free survival; *PR*, partial response; *PUVA*, psoralen plus ultraviolet A; *q*, every; *qd*, once daily; *qod*, every other day; *qowk*, every other week; *S*, skin; *SC*, Sézary cells; *SQ*, subcutaneous; *SS*, Sézary syndrome; *T₄*, erythrodermic stage (mycosis fungoides or Sézary syndrome); *tiw*, 3 times weekly; *TSEBT*, total skin electron beam radiation; *UNK*, unknown; *UV*, ultraviolet; *V*, viscera.

Levels of evidence[45]: I = evidence obtained from at least one properly randomized controlled trial; II-1 = evidence obtained from at least one well-designed controlled trial without randomization; II-2 = evidence obtained from at least one prospective, well-designed cohort or case-control study, preferably from more than one center or research group; II-3 = evidence obtained from at least one retrospective, well-designed cohort or case-control study, preferably from more than one center or research group; III = evidence obtained from multiple time series with or without intervention; IV = includes opinions of respected authorities, based on clinical experience, descriptive studies, and case reports or reports of expert committees.

Publications included must have described Food and Drug Administration—approved treatment, definition of SS used, dosing regimen used, and had definition of response as ≥50% clearance from baseline. In cases where definition of SS was not specifically given, extrapolation could be made from history that subjects likely met current criteria of SS.

Table III. Allogeneic bone-marrow transplantation

Reference	No. of SS/total patients in study	Stage before transplantation	Age (y)/sex	Prior treatments	Conditioning	Myeloablative	Type of transplantation	Response duration	Response*	Last f/u	Outcome	Study type
Duvic et al[311]	3/19	SS/IVB ($T_4N_{0-3}M_{-1}B_2$)	21, 58/F; 48/M	Retinoid, interferon alfa ± systemic chemotherapy and/or ECP	TSEBT/Flu/Mel or TSEBT/ Flu/Cy/ Rituxan	No	Allo sibling-matched PBSCT	≥14, ≥22, ≥91 mo	100% CR (3/3)	14, 22, ≥91 mo	Alive; CR with acute skin GvHD 3/3, chronic skin + liver or GI GvHD	Retrospective cohort study
	3/19	SS/IVA-B ($T_4N_{0-3}M_{-0-1}B_2$)	50, 53/F; 41/M	Retinoid, interferon alfa ± systemic chemotherapy or ECP	TSEBT/Flu/ Mel	No	Allo sibling-matched PBSCT	1, 13, 14 mo	67% CR (2/3 CR; 1/3 PD)	9, 13, 27 mo	Deceased with sepsis: chronic skin, GI ± multiple organ GvHD	
	1/19	SS/IVA-IVB ($T_4N_{0-3}M_{0-1}B_2$)	60/M	Retinoid, interferon alfa, ECP	TSEBT/Flu/ Mel	No	Allo sibling matched; ? origin SCT	20 mo	100% CR (1/1)	20 mo	Alive in CR: no GvHD	
	3/19	SS/IVA-IVB ($T_4N_{0-3}M_{0-1}B_2$)	36, 61/M; 51/F	≥4 Systemic therapies (varied)	TSEBT/Mel/ ATG ± Flu	No	Allo MUD PBSCT	7, ≥14, ≥26 mo	100% CR (3/3)	19, 14, 26 mo	Alive; 2/3 in CR; 1 acute liver, skin GvHD, 2/3 chronic cutaneous GvHD, 1/3 no GvHD	
	3/19	SS/IVA-IVB ($T_4N_{0-3}M_{0-1}B_2$)	48-55/M	Retinoid, interferon alfa, ECP ± anti-CD4, HDACi, systemic chemotherapy	Flu/ATG ± Bu, TSEBT, Mel	No	Allo MUD BMSCT	1.5, ≥44, ≥89 mo	2/3 CR, 1/3 PR	5, 44, 89 mo	2 Alive in CR at 44 and 89 mo both with acute/chronic skin and 1 with widespread GvHD, 1 dead at 5 mo with acute/chronic skin GvHD	
	1/19	SS/IVB ($T_4N_{0-3}M_{-1}B_2$)	46/F	Retinoid, interferon alfa, ECP, Ontak, systemic chemotherapy	TSEBT/Flu/ Cy/ATG	No	Allo	2 mo	100% CR (1/1)	99 mo	Alive PR; acute skin and chronic skin/lung/eye GvHD	

Continued

Table III. Cont'd

Reference	No. of SS/total patients in study	Stage before transplantation	Age (y)/sex	Prior treatments	Conditioning	Myeloablative	Type of transplantation	Response duration	Response*	Last f/u	Outcome	Study type
Molina et al[312,313]	1/8	SS/IVA[†] ($T_4N_3M_0B_2$)	22/F	MTX, PUVA, ECP, hydroxyurea, interferon alfa, 2-CDA	FTBI 13.2 Gy/Cy 60 mg/kg × 2 d	Yes	Allo MUD BMT	≥ 108 mo	100% CR between d 30 and 60 (clinical, molecular remission in skin, blood, nodes, BM, and cytogenetic)	109 mo	Alive; CR with extensive chronic skin GvHD	Case report and retrospective cohort study
Molina et al[312]	2/8	SS/IVA[†] ($T_4N_3M_0B_1$)	21	PUVA, CSA, interferon alfa, ECP, TSEBT, 2-CDA	Bu 16 mg/kg IV q 6 h × 16/Cy 60 mg/kg × 2 d	Yes	Allo sibling-matched PBSCT	≥ 60 mo	100% CR between 20-60 d (skin, nodes, blood)	60 mo	Alive; CR with limited chronic skin GvHD	Retrospective cohort study
		SS/IIIA[†] ($T_4N_0M_0B_1$)	59	PUVA, MTX, interferon alfa, ECP, bexarotene, gemcitabine, 2-CDA	Flu 25 mg/m² qd × 5 d/Mel 140 mg/m² × 1 d (Flu/Mel)	No	Allo sibling-matched PBSCT	≥ 53 mo	100% CR skin between 30-60 d (skin , nodes, blood)	53 mo	Alive; CR with extensive chronic skin GvHD	Retrospective cohort study
Cudillo et al[316]	1/1	SS/IVA[‡] ($T_4N_xM_0B_2$)	56/F	ECP, interferon alfa, steroids, alemtuzumab	Flu 80 mg/m²/ thiotepa 10 mg/kg and Cy 60 mg/kg	No	Allo sibling-matched PBSCT	24 mo after DLI	No clearing with transplantation alone; DLI at 14 and 15 mo, CR at ≥ 23 mo (clinical, molecular remission; skin, blood)	36 mo	Alive; CR with limited chronic skin GvHD	Case report
Kahata et al[317]	1/1	SS/IVB[‡] ($T_4N_3M_1B_2$) with LCT	22/M	PUVA, CHOP, 46-Gy TSEBT	TBI (2 Gy) × 1 d Flu 25 mg/m² × 5 d/Mel 140 mg/m² × 1 d	No	Allo MUD BMT	≥ 36 mo	100% CR on d 17 (clinical, molecular remission)	36 mo	Alive; CR with extensive chronic systemic GvHD and membranous GN	Case report

Herbert et al[318]	1/3	SS/IVB[†] (T$_4$N$_3$M$_1$B$_2$)	51/M	PUVA, TSEBT, MTX, liposomal doxorubicin, Cy	Flu 25 mg/m^2 × 5 d/Mel 140 mg/m^2 × 2 d	No	Allo sibling-matched PBSCT	Uncertain	PR only including with DLI	11 mo	Died at 11 mo of chronic GvHD (pneumonitis) and PD	Case series
Soligo et al[319]	2/3	SS/IVA[‡] (T$_4$N$_3$M$_0$B$_2$)	60/M	PUVA, interferon alfa, MTX, ECP, steroids, alkylating agents, Flu, rituximab	Flu 30 mg/m^2 × 3 d repeated 28 d/TBI × 1 d	No	Allo sibling-matched PB CD34$^+$	≥21 mo	NR at 2 mo; 100% CR at 3 mo to acute GvHD (clinical, molecular remission in skin and blood)	24 mo	Alive; CR without GvHD	Case series
		SS/IVA[‡] (T$_4$N$_X$M$_0$B$_2$)	51/M	ECP, steroids, MTX	2 Cycles Flu, 30 mg/m^2 × 3 d/Cy 300 mg/kg × 3 d, TBI × 1 d	No	Allo sibling-matched PB CD34$^+$	≥16 mo	CR on d 58 (clinical, molecular remission in skin and blood)	18 mo	Alive; CR with limited chronic GvHD	

Allo, Allogeneic; *ATG,* antithymocyte globulin; *BM,* bone marrow; *BMT,* bone-marrow transplantation; *Bu,* busulfan; *CD34$^+$,* CD34-enriched PBSCT; *CDA,* chlorodeoxyadenosine; *CHOP, Cy,* Adriamycin, vincristine, and prednisone; *CR,* complete response; *CSA,* cyclosporine; *Cy,* cyclophosphamide; *DLI,* donor lymphocyte infusion; *ECP,* extracorporeal photopheresis; *F,* female; *Flu,* fludarabine; *FTBI,* fractionated total body irradiation; *f/u,* follow-up; *GI,* gastrointestinal; *GN,* glomerulonephritis; *GvHD,* graft-versus-host disease; *HDACi,* histone deacetylase inhibitor; *IV,* intravenous; *LCT,* large cell transformation; *M,* male; *Mel,* melphalan; *MTX,* methotrexate; *MUD,* matched unrelated donor; *NR,* no response; *PB,* peripheral blood; *PD,* progressive disease; *PR,* partial response; *PUVA,* psoralen plus ultraviolet A; *q,* every; *qd,* once daily; *SCT,* stem cell transplantation; *SS,* Sézary syndrome; *TBI,* total body irradiation; *TSEBT,* total body electron beam radiation.

[+]Fourteen patients with SS in tables (presented here), 11 patients with SS in text.

Studies included only if they reported dosing regimen, definition of SS, and definition of response as ≥50% improvement from baseline.

*Response lasting at least 1 mo.

[‡]International Society for Cutaneous Lymphomas/European Organization for the Research and Treatment of Cancer definition SS, ie, T$_4$B$_2$.

[†]Mycosis Fungoides Cooperative Group staging SS, ie, T$_4$B$_1$ ≥ 5% SC.

Table IV. Treatment recommendations for Sézary syndrome

Primary treatment	Secondary treatment (after inadequate response, refractory disease, or progression despite primary treatments)

• Category A systemic therapies (monotherapies)
   o ECP
   o Interferon alfa
   o Bexarotene
   o Low-dose methotrexate ($\leq$ 100 mg/wk)
   o Denileukin diftitox (plus corticosteroid)
 	
• Category A combination therapies
   o Systemic + SDT*
      ■ Interferon alfa or gamma + PUVA or topical nitrogen mustard
      ■ Methotrexate (low dose) + topical nitrogen mustard
      ■ Bexarotene + PUVA
      ■ Immunomodulators (ECP, interferon alfa or gamma, bexarotene singly or in combination) + TSEBT
 	
   o Systemic + systemic
      ■ Interferon alfa + bexarotene
      ■ ECP + other immunomodulators (bexarotene, interferon alfa, interferon gamma, low-dose methotrexate singly or in combination)
      ■ Methotrexate (low dose) + interferon alfa
	• Category B systemic therapies (decision as to what order to use must take into account blood tumor burden, patient age and overall health, prior therapies)
	   o Alemtuzumab
	   o Chlorambucil + corticosteroid
	   o Liposomal doxorubicin
	   o HDAC inhibitors
	      ■ Vorinostat
	      ■ Romidepsin
	   o Gemcitabine
	   o Deoxycoformycin
	   o High-dose methotrexate (>100 mg/wk)
	   o Fludarabine $\pm$ cyclophosphamide
	   o Mechlorethamine
	   o Consider allogeneic transplantation as appropriate
	   o Clinical trial

ECP, Extracorporeal photopheresis; *HDAC*, histone deacetylase; *PUVA*, psoralen plus ultraviolet A; *SDT*, skin-directed therapy; *TSEBT*, total skin electron beam radiation.
Modified from National Comprehensive Cancer Network guidelines.[46] The only treatments included here are those that are Food and Drug Administration approved and have published data demonstrating at least 20% response rate in Sézary syndrome.
*Topical corticosteroids are reasonable SDT used with any systemic therapy.

alfa-2b tiw but scant data preclude more specific comments on response. Nicolas et al[65] reported improvement in patients with SS treated with interferon alfa 40 MU/wk for 6 months. Dreno et al[66] reported on 13 cases of SS treated with interferon alfa 6 to 9 MU once daily (qd) for 2 to 3 months then tiw for 10 months with an OR in 25% (3 of 12) of these compared with 60% (12 of 20) with early-stage MF. Other publications of patients with SS (where criteria was specifically defined) treated with interferon alfa are presented in Table I.[61,67]

Interferon alfa in combination with psoralen plus ultraviolet (UV) A (PUVA) has shown efficacy in E-MF (blood involvement unspecified)[56,68-70] but there was not been a uniform response in the two patients with SS reported.[71,72] Interferon in combination with retinoids (isotretinoin, etretinate, bexarotene) has been noted to be effective in late-stage MF/SS[73-77] but, to our knowledge, there are no studies where the combination is compared with monotherapy alone and none where the results in SS are specifically addressed. Patients with SS treated with a combination of interferon alfa and pentostatin[78] or interferon alfa and fludarabine[79] demonstrated ORs but the overall response rate (RR) in all patients with MF thus treated (41% and 51%, respectively) was not higher than that seen in other studies with interferon alone.[47,52] In the case of patients treated with interferon alfa and extracorporeal photopheresis (ECP), there has been an overall excellent response to combination therapy in those with SS[80-84] and an improvement in response to ongoing ECP with the addition of interferon alfa in individual patients with SS.[85,86] The only prospective study comparing interferon alfa alone with combination interferon alfa/ECP in various stages of MF/SS, however, failed to show any improvement with the combination over interferon alfa

monotherapy[47] raising the question of whether there is truly an additive or synergistic effect of combination ECP and interferon alfa and calling for a prospective randomized clinical trial to address this.[87] Positive results have been reported in patients with SS treated with multimodality immunomodulatory therapy with interferon alfa 3 to 9 MU tiw (maximum tolerated dose), ECP on 2 consecutive days every 2 to 4 weeks, PUVA tiw, and topical steroids with a RR of 42% (5 of 12) including a CR in one of 12.[88]

It is of value to highlight the results of a large single-site trial of interferon alfa and methotrexate (MTX) that included patients with SS but did not selectively present their results and thus are not presented in Table I. Aviles et al[89] treated 158 patients with stage IIB to IVA MF/SS with MTX 10 mg/m^2 twice a week (biw) plus interferon alfa-2a 9 MU tiw × 6 months: those with PR continued for another 6 months on interferon and MTX and those with a CR at 6 or 12 months continued only on interferon. The results were impressive: 49% CR at 6 months and 49% additional CR at 12 months for a total of 74% CR. Mean duration of response (MDR) was not given but the 10-year estimated survival was 69%. Toxicity was mild, grade 1 in most cases, and only 3 of 158 patients had any hepatic enzyme elevations (all mild). This paucity of adverse effects was all the more unusual given both the relatively high dose of interferon and MTX and no folic or folinic acid given in conjunction with the latter. All publications using interferon alfa in combination with other therapies for the treatment of SS are shown in Table II.[72,79-86,88,90-97]

Acute side effects of interferon alfa include fever, chills, myalgias, and headache that usually dissipate over the first week of therapy and are minimized by pretreatment with acetaminophen. The common chronic side effects seen with interferon alfa include fatigue, anorexia, weight loss (generally 5-10 lb), depression, or change in cognitive function.[52] The latter is generally more severe in the elderly. The adverse effects are generally dose related and may decrease over time. Thyroid dysfunction, primarily hypothyroidism, may develop in up to 20% of patients receiving interferon alfa and may be the cause of some of the fatigue, especially if it escalates during therapy. Cardiac toxicity has been reported with higher doses of interferon alfa than generally used for CTCL but patients with a history of coronary artery disease, especially those with any recent acute events, should be carefully monitored. Less common effects include loose stools, peripheral neuropathy, and altered (metallic) taste. An increase in liver function test results is very common but is generally mild and does not generally require dose adjustment. Myelosuppression is also common with the nadir at 1 to 3 weeks for leukocytes and 4 weeks for platelets but absolute neutropenia is rare and changes do not usually require intervention other than dose reduction. All changes are reversible off drug. There are no long range cumulative dose effects and no increased incidence of second malignancies with interferon alfa so that long-term treatment is reasonable.

Interferon gamma

Recombinant interferon gamma-1b (Actimmune) is a type 2 interferon that acts as a biological response modifier.[98] Similar to type 1 interferons, IFN-γ plays an important role in immunoregulation. It is currently FDA approved for chronic granulomatous disease and osteopetrosis but its use in CTCL was first reported in 1990.[99] In CTCL, IFN-γ enhances cell-mediated cytotoxicity of CD8$^+$ T cells and NK cells, primes DCs, inhibits tumor cell proliferation and Th2 cytokine production, and inhibits Tregs.[20]

Unlike interferon alfa, publications of the use of interferon gamma in CTCL and SS are extremely limited. Kaplan et al[99] reported 16 patients with CTCL and stage IB to IVB treated with interferon gamma with a RR in 31% of patients including one of two with SS (Table I). Publications citing the use of interferon gamma in combination with other biologic response modifiers is shown in Table II.[100-102] Shapiro et al[100] reported a patient with SS who had progressive disease on interferon gamma and ECP who went on to a durable CR with the addition of bexarotene and PUVA. McGinnis et al[101] also showed a long-lasting clearing of disease in a patient with SS treated with a combination of interferon gamma, ECP, and bexarotene. More recently, adenovirus-mediated intralesional interferon gamma gene transfer in CTCL and cutaneous B-cell lymphoma was studied in phase I and II clinical trials.[103] Three patients with MF and two with SS were treated in a dose escalation trial of 3×10^9 to 3×10^{11} intramuscularly 3/4 weeks per monthly cycle: two of 3 patients with MF had a response in the lesion treated but neither of the patients with SS responded. Shimauchi et al[104] treated 12 patients with MF (4 with erythroderma, rest with plaque disease) with interferon gamma −0.25 to 0.5 MU qd 5/7 days per week × 1 to 4 weeks in conjunction with narrowband UVB (NBUVB) tiw. All but one patient was a responder and 4 of 12 (25%) had a CR. There was no information on median response duration (MRD). Clinical responses to interferon gamma have been observed in interferon alfa nonresponders.[99]

Adverse effects of interferon gamma are similar to those observed for interferon alfa but are notably milder: low-grade fever, flu-like symptoms, headache, myalgias, fatigue, nausea, weight loss, cognitive effects, dose-dependent cytopenia (usually neutropenia), hepatic transaminitis, nonscarring alopecia, and less commonly, triggering of autoimmune phenomenon (eg, thyroiditis, hepatitis, nephritis, psoriasis). An urticarial reaction to interferon gamma has been documented.[99] Elderly patients appear to tolerate interferon gamma better than interferon alfa in terms of cognitive effects (depression, confusion). Two of the authors (E. Kim, MD, and A. Rook, MD, unpublished data) have noted lot-to-lot variation in regard to the adverse effect of fever seen with interferon gamma: it is possible that some lots may contain higher levels of endotoxin after the production process.

Retinoids

Bexarotene (Targretin). Bexarotene is a novel synthetic rexinoid that binds selectively to the retinoid X receptor (RXR) isoforms (RXR α, β, and γ). The RXRs form heterodimers with various other nuclear hormone receptors including retinoic acid (RA) receptors (RARs), the vitamin-D receptor, thyroid hormone receptor, peroxisome proliferator activator receptor, liver X receptor, and farsenoid X receptor, which in turn act as ligand-inducing transcription regulatory factors.[105] Retinoids have been shown to affect the malignant cells by inhibition of tumor cell proliferation, promotion to terminal differentiation, and induction of apoptosis.[105,106] Bexarotene may also work through the down-regulation of Th2 cytokines,[106] by inhibiting malignant cell trafficking to the skin through an ability to suppress CCR4 expression among malignant lymphocytes[107] or through down-regulation of E-selectin on endothelial cells, thus causing the entrapment of cutaneous homing T lymphocytes in the circulation.[108] The exact mechanism of action in CTCL is unknown. Bexarotene was FDA approved in 1999 as 75-mg soft gelatin capsules for the treatment of refractory CTCL. It is highly protein bound, eliminated primarily through the hepatobiliary system, and appears to be metabolized to oxidative forms by the cytochrome p450 3A4 isozyme, the latter of which could lead to an increase or decrease in blood levels of bexarotene when taken with other drugs that are inhibitors or inducers of CyP 4503A, respectively.[105,109]

Bexarotene has been studied in late-stage CTCL in a large multicenter phase II to III trial.[110] Of 94 patients with stage IIB or higher MF/SS, 45% (25 of 56) of those patients begun on 300 mg/m^2/d had an OR (including 2% [one of 56] with a CR) compared with 55% (21 of 38) OR in those patients begun on more than 300 mg/m^2/d (including 13% [5 of 38] CR). There was a RR of 24% (4 of 17) in those with SS. The St Johns Hospital group in London, England reported on 28 patients with stage IB or higher MF/SS who were treated with bexarotene monotherapy 150 to 300 mg/m^2/d escalating to 300 mg/m^2/d: the RR was 46% (13/28) including 14% (4/28) CR and was highest in those with SS.[111] The patients with SS treated with bexarotene monotherapy are reported in Table I.[110-114]

Tsirigotis et al[115] noted a 100% RR in 3 patients with MF and two with SS treated with a combination of ECP and bexarotene, and Ranki[91] noted a PR in one patient with SS treated with a combination of interferon alfa and bexarotene. Richardson et al[92] noted an 89% RR rate in 28 patients treated with ECP, interferon alfa, and—in 24 of 28 cases—bexarotene. McGinnis et al[95] treated two patients with SS with a combination of ECP, interferon gamma, bexarotene, and PUVA with resulting one CR and one PR. They also reported on two patients with SS treated with a combination of ECP, interferon alfa-2b, and bexarotene who went on to a CR (A. Rook, MD, unpublished data) and one patient with SS treated with a combination of interferon gamma, ECP, and bexarotene who went onto a CR only on the addition of PUVA, highlighting again the efficacy of PUVA in MF/SS, even in systemic disease. Although there are several case reports of patients with all stages of MF who have had an OR to a combination of bexarotene and PUVA,[116-119] there are no reports to date of efficacy in SS. There have been several reports, primarily in patients with SS, of acute worsening or more aggressive disease (large cell transformation, extracutaneous disease, CD8+ lymphoma) after starting bexarotene: the causality is not clear in these cases.[93,101,113,114,120] Also noted has been an improvement in the skin with bexarotene treatment while either no change or worsening of the blood tumor burden has occurred.[91,121,122] Publications using bexarotene in combination with other therapies in the treatment of SS are shown in Table II.[91,93,95,96,100,101,113,115]

The two most common side effects of bexarotene include hyperlipidemia and central (secondary) hypothyroidism.[109] In patients taking 300 mg/m^2/d or more of bexarotene, 60% developed cholesterol more than 300 mg/dL and 70% developed more than 2.5 times the normal level of triglycerides including 55% with triglycerides over 800 mg/dL. Central hypothyroidism occurred in ~40% of patients during the clinical trials but is observed in nearly all patients in clinical practice. Expectant

treatment for these two side effects is necessary and treatment with antilipid agents ± thyroid supplements begun before or concomitant with bexarotene is necessary in most cases with close monitoring and adjustment of doses of ancillary drugs over the first 4 to 8 months of treatment. Certain antilipid agents (atorvastatin or fenofibrate) are preferable: gemfibrozil is to be avoided secondary to increased levels of bexarotene and thus triglycerides. Dose-related leukopenia occurs in more than 10% of patients and neutropenia can be dose limiting. Other side effects include fatigue, asthenia, headache, anemia, nausea, peripheral edema, photosensitivity, diarrhea, dry skin, and rash. Hypoglycemia has been noted especially in patients on insulin-secreting medications or insulin sensitizers. Infections are uncommon with bexarotene. All retinoids are pregnancy category X and women of childbearing potential must use two effective methods of contraception for a month before, during, and 1 month after discontinuation of drug. Male patients should use condoms during sexual intercourse while on bexarotene and for 1 month after stopping the drug.

RAR retinoids. The retinoids isotretinoin, etretinate, acitretin, and all-*trans*-RA (ATRA) all work through transcriptional changes induced in the RARs.[123] The RARs, including the isozymes RAR *α*-1 and -2, *β*-1 to -4, and *γ*-1 and -2, form heterodimers with each other and with RXRs: these bind to RA response elements in the cell nuclei, which in turn bind to DNA and interact with other transcription factors.[124] RARs do not bind to the other nuclear hormone receptors as does bexarotene and their side-effect profile is, not surprisingly, different from that of bexarotene. RAR retinoids can induce IFN-γ, partially through IL-12, which may produce a shift from a Th2 to Th1 cell predominance, up-regulate Langerhans cell antigen presentation and surface expression of HLA-DR and CD11 involved in T-cell activation, and enhance cytotoxic activity of NK cells.[123,124] RAR retinoids have antiproliferative, antiangiogenic, and immunomodulatory effects and modulate cellular differentiation.[124]

Isotretinoin (Amnesteem, Claravis, Sotret). Isotretinoin (13-*cis*-RA) was the first retinoid used in MF/SS: it is FDA approved for the indication of severe recalcitrant nodular acne. Its absorption is increased with food or milk and it is metabolized to both RA, with which it is reversibly interconverted, and oxidized forms. Terminal elimination half-life is 21 hours with excretion in the urine and feces.[109]

Isotretinoin has shown efficacy as monotherapy[125-130] in both tumor- and plaque-stage MF at doses of ~1 to 3 mg/kg/d. Kessler et al[125] treated 4 patients with MF and either extensive plaque or erythroderma with 1 to 3 mg/kg/d of isotretinoin with an OR in all. Kessler et al[128] treated an additional 25 patients with MF, 7 whom had erythroderma and 5 with more than 5% SC but no documented SS, with isotretinoin 1 to 2 mg/kg/d: there was a 44% OR including 4 of 7 with erythroderma. Three of the 25 had a CR (stage unspecified) and MRD was greater than 8 (1-25) months. The Scandinavian Mycosis Fungoides Group treated at least 39 patients with isotretinoin (reported in two different publications)[129,130]: the OR in MF/SS to isotretinoin 0.2 to 2 mg/kg/d was 59% including one of 5 SS (blood involvement not noted).[129] Because of the uncertainty of the definition of SS used in reports, the efficacy of isotretinoin in SS is unknown.

Common side effects of isotretinoin include dry skin, cheilitis, dry eyes, arthralgias, myalgias, elevated liver function test results, and mild alopecia.[109] Elevation of triglycerides is common (generally mild but marked elevations have been reported) and lipids must be monitored during therapy. Pseudotumor cerebri; mood changes, especially depression; changes in bones (including diffuse idiopathic skeletal hyperostosis); hearing problems; and decrease in night vision have been reported. As with all retinoids, the use of isotretinoin is contraindicated in pregnancy. Women of childbearing potential and men with sexual partners of childbearing potential are mandated to take special contraceptive precautions including monthly pregnancy tests for women at risk of pregnancy.

Etretinate (Tegison) and Acitretin (Soriatane). Etretinate was FDA approved for the treatment of psoriasis and was also used in several pre-bexarotene trials of MF/SS. It was withdrawn from the market in 1998 but its metabolite, acitretin, was approved in its place, again for psoriasis. Etretinate was replaced by acitretin because of its long half-life, protracted tissue storage time, and thus prolonged risk of teratogenicity in women. After oral absorption, which is increased with food, acitretin is interconverted to its 13-*cis* form (*cis*-acitretin) and both further metabolized to short chain conjugates and breakdown products that are eliminated in the feces and urine. The terminal elimination half-life of acitretin is 49 hours. When taken with alcohol, acitretin undergoes transesterifcation to etretinate.

Etretinate has shown efficacy as monotherapy[129,131,132] in the treatment of MF and SS. Claudy et al[132] used etretinate 0.8 to 1 mg/kg/d to treat 6 patients with MF (3 with erythroderma, one with SS, one with extensive plaque, one with tumors and blood involvement [>10% SCs]). Five of the 6 patients clinically "cleared" including the one patient with SS but there was no histologic clearance

in the skin. Molin et al[129] reported on 7 patients with advanced disease (5 tumor-stage MF, one with nodal disease, and one SS) who were treated with etretinate 0.2 to 1 mg/kg/d: there was an OR in 4 of 7 patients with MF but no response in the patient with SS. When they compared all stages of patients with MF/SS treated with either etretinate (n = 29) or isotretinoin (n = 39), there was no significant difference in overall RR (66% vs 59%, respectively) between the two retinoids.[129] Acitretin has also shown usefulness in all stages of MF as monotherapy.[133-135] Mahrle et al[135] saw a response in 3 of 4 patients with MF treated with acitretin but not in the patient identified as having SS (no information on blood involvement given). As with other retinoids, acitretin has been shown to be less effective than interferon alfa when used in combination with PUVA to treat patients with MF.[136] Since the approval of bexarotene for MF, there have been few additional studies using these RAR retinoids in MF/SS.

Common side effects of etretinate/acitretin include elevated liver function test results, increase in serum lipids (especially triglycerides), dry eyes, dry skin, cheilitis, alopecia, nail abnormalities including paronychia, "sticky skin," arthralgias, and hyperostosis. As with all retinoids, the use of acitretin is contraindicated in pregnancy. Women of childbearing potential and men with sexual partners of childbearing potential are mandated to take special contraceptive precautions during and for 3 years after therapy for the women at risk.

ATRA (Vesanoid). The natural retinoids such as ATRA (tretinoin) and its isomers 9-*cis*-RA (alitretinoin) and 13-*cis*-RA (isotretinoin) are nonselective agonists.[109,137] Although ATRA binds only with RAR, and 9-*cis*-RA binds with both RAR and RXR, all 3 ligands activate RAR and RXR as a result of isomerization. ATRA is a natural retinol metabolite formed by enterocytes from B-carotene and from tissue metabolism of vitamin A (retinol) and retinaldehyde in an enzymatic process that requires nicotinamide-adenine-dinucleotide phosphate.[138] Cytochrome P450 enzymes have been implicated in the oxidative metabolism. Its metabolites include 13-*cis*-RA, 4-oxo-*trans*-RA, 4-oxo-*trans*-RA glucuronide, and 4-oxo-*cis*-RA. The in vitro biologic action of ATRA includes induction of apoptosis, induction of IFN-γ, and IL-12 production and enhancement of cell-mediated immunity.[139] ATRA is FDA approved for acute promyelocytic leukemia as a 10-mg capsule formulated in an oil suspension with absorption primarily through the portal route. ATRA is rapidly metabolized to a variety of oxidized or conjugated metabolites and does not accumulate in any tissue. The terminal half-life is under 1 hour with a gradual

decrease seen in plasma levels with chronic dosing. Of note, ATRA blood levels have been shown to be higher with concomitant interferon alfa dosing than ATRA monotherapy.[140]

The biologic effects of ATRA were reported in 33 patients with MF/SS (12 stage IB or IIA and 21 stage IIB-IVA) with an overall RR of 12% including one of 33 CR.[141] Seventeen of these patients had SS by T_4B_1 Mycosis Fungoides Cooperative Group staging[6] with 24% OR including one of 17 CR (C. Querfeld, MD, unpublished data). The MRD is unknown.

Common reported adverse effects of ATRA include dry skin and mucous membranes, and constitutional symptoms such as fatigue, arthralgias, and myalgias that often require dose reduction.[141] Irritability and mild to moderate headaches including those secondary to pseudotumor cerebri have also been seen with ATRA. The most common laboratory changes are reversible, dose-dependant, asymptomatic hypertriglyceridemia and elevated liver function test findings. In patients with acute promyelocytic leukemia (APL), but so far not in patients with MF, an RA-APL syndrome characterized by fever, pulmonary infiltrates, and potential multiorgan failure has been seen in as many as 25% of patients.[109] As with other retinoids, ATRA is a teratogen and precautions to prevent pregnancy in women of childbearing potential should be undertaken.

Denileukin diftitox

Denileukin diftitox is a recombinant DNA-derived fusion protein containing the peptide sequences for the enzymatic activity and membrane translocatory domains of diphtheria toxin followed by sequences from human IL-2. The drug brings the cytocidal action of diphtheria toxin to cells with expression of the medium and high affinity IL-2 receptors (CD122/132 and CD25/122/132). After interaction with the receptor, the drug is internalized, the toxin is released to the cytosol after cleavage in the endosome and inhibition of protein synthesis (via adenosine diphosphate ribosylation of elongation factor 2) leads to the cell's death.[142] Denileukin diftitox is approved for the treatment of CD25$^+$ CTCL.

In a multicenter phase I dose escalation trial of 35 patients with CTCL (30 with MF, 4 with large cell CTCL, and one with T-cell lymphoma not otherwise specified), denileukin diftitox 6 to 31 μg/kg/d was given in a 5- to 15-minute intravenous (IV) infusion repeated every 3 weeks.[143] The overall RR for stages I to IV was 37% (14% CR, 23% PR) with a lower OR in advanced-stage patients (2/7 [29%] stage III and 0/10 stage IV): no patients with SS were specifically reported. In the phase III multicenter study of 71 patients with MF/SS where the dose of denileukin

diftitox was randomized to 9 or 18 μg/kg/d $\times$ 5 days repeated every 3 weeks, there was an overall 10% CR and 20% PR.[142] There was also a higher RR in those with early (stage IB-IIA) compared with advanced (stage $\geq$ IIB) disease (RR of 43% vs 10%) treated with the lower 9-μg/kg/d dose of denileukin diftitox but increased RR in advanced disease with the 18-μg/kg/d dose (RR of 33% in stage IB-IIA and 38% RR in $\geq$ stage IIB). Although there were patients in this study who had erythrodermic (T_4) skin disease and blood involvement as defined by more than 20% $CD4^+/CD7^-$ peripheral blood cells, patients with SS were not specifically identified or noted among the responders. In a phase III multicenter placebo-controlled study of 144 patients with MF/SS stage IA to III (using TNM staging system) where the dose of denileukin diftitox was randomized to 9 or 18 μg/kg/d $\times$ 5 days repeated every 3 weeks, there was a CR/OR rate of 9.1%/49.1%, 11.1%/37.8%, and 2.3%/15.9% for the 18-μg/kg/d dose of denileukin diftitox versus 9-μg/kg/d dose of denileukin diftitox versus placebo, respectively.[144] Patients with SS were not specifically identified or results reported in this publication.

Higher RRs were noted in trials where corticosteroids were used as premedication: as these were the only studies where patients with SS were specifically noted, they are listed in Table I.[145,146] The phase I dose escalation trial of denileukin diftitox reported by Chin and Foss[146] used 4 to 9 μg/kg/d $\times$ 5 days the first cycle then escalated to 18 to 27 μg/kg/d thereafter along with premedication with Decadron 8 mg. The 29 patients with advanced-stage MF ($\geq$ IIB) had a RR of 48% compared with 63% of patients with earlier disease stages. Foss et al[145] reported on a retrospective review of 7 patients with MF and 8 with SS (T_4 skin disease plus circulating $CD4^+/CD7^-$ lymphocytes) treated at two institutions with 9 or 18 μg/kg/d denileukin diftitox for the first cycle then 18 μg/kg/d in subsequent cycles plus either 20 mg prednisone or 8 mg Decadron with each infusion. An OR was seen in 5 of 7 (71%) patients with MF and 4 of 8 (50%) patients with SS. The combination of denileukin diftitox 18 μg/kg/d and Decadron 8 mg $\times$ 3 days every 21 days along with cohort escalations of bexarotene from 75 to 300 mg every day was used to treat 14 patients with MF stages I to IVA with a RR of 67% (4/14 CR, 4/14 PR).[147] No patient with SS was identified in the latter study.

Acute side effects of denileukin diftitox include hypersensitivity reactions such as dyspnea, chest tightness, hypotension, chills, fever, pruritus, flushing, rash, tachycardia, dysphagia, and/or back pain; a flu-like reaction characterized by fever, asthenia, myalgia, and/or arthralgia; and gastrointestinal (GI) symptoms including nausea, vomiting, and/or diarrhea. Delayed toxicities include a vascular leak syndrome (hypoalbuminemia and/or edema and orthostatic hypotension) that occurs in up to 25% of patients, transient transaminase elevation and lymphopenia, rash, thromboses, rarely hyperthyroidism, possible elevated risk of infection,[142] and uncommon visual impairment.[109] There is a decreased incidence of side effects, especially dyspnea and edema, seen with steroid premedication.[145] It is advised that the infusion of the drug should be undertaken over 60 minutes to minimize infusion reactions. Consideration should be given to treating severe edema associated with severe hypoalbuminemia with albumin replacement.

Extracorporeal photopheresis

ECP is an apheresis procedure that targets the circulating malignant clone in patients with CTCL. The procedure currently performed uses liquid 8-methoxypsoralen injected directly into a collection bag containing an enriched white blood cell (WBC) fraction. After photoactivation of the WBC fraction with UVA energy, all treated and untreated blood products are returned to the patient. Patients with MF or SS are usually treated on two consecutive days at 4-week intervals. The immunomodulatory mechanism underlying patient responses to ECP is still unfolding. However, evidence currently supports the following two simultaneous and synergistic processes occurring during ECP: induction of apoptosis in malignant T cells and a conversion of blood monocytes to DCs. Together these processes induce an immune response against the malignant clone.[148-150]

Efficacy in treating certain clinical stages (IB, IIA, III, and IVA) and skin stages (patch/plaque [T_2] and erythroderma [T_4]) of MF and SS with ECP is favorable, although randomized trials comparing ECP with other standard therapies are needed.[148-150] The overall RR for ECP monotherapy has ranged from 36% in an intention-to-treat analysis[149] to 10%, 17%, 50%, 80%, and 83% in those patients with MF/SS who have been on ECP for at least 3 months.[84,90,149,151] Edelson et al[152] reported a response ($\geq$ 25%) in 83% (24 of 29) of patients with E-MF (blood involvement not given). Those studies in which SS has been clearly defined and an OR defined as at least 50% clearing are shown in Table I.[84,90,151,153-158] However, there are notable publications where response in patients with SS to ECP (given as 2 consecutive days monthly) is defined only as at least 25% clearing. Not surprisingly, the RR is higher in these cases: de Misa et al[158] reported on 60% response in the skin in 10 patients with SS (defined as T_4 + >5% peripheral blood SC + clonal involvement) and Evans et al[159] noted a

response in skin in 57% of patients with SS (defined stringently as T$_4$, ≥10% peripheral blood SC, and clonality TCR gene rearrangement). Duvic et al[149] used an accelerated protocol for ECP (9 vs 6 cycle collection and increased frequency from the standard two treatments per month in the case of nonresponders) and noted inclusion of 20 of 34 patients with peripheral blood SCs (not specifically SS) with an OR in 50% of all patients including a CR in 18%. A recent consensus statement from the United Kingdom recommends that all patients with erythrodermic CTCL, either stage III or IVA (major criteria), who have one or more minor criteria of a peripheral blood T-cell clone, more than 10% SCs, and/or CD4/CD8 ratio higher than 10 should be considered for ECP therapy.[160] There are data to suggest that response is better in those who have not been immunosuppressed by chemotherapy (A. Rook, MD, unpublished data) and among those who have a lower blood tumor burden[156,161,162] or the absence of bone-marrow involvement.[158] There is also evidence to show a potential disconnect between clearance of disease in the skin and blood.[81] Fraser-Andrews et al[163] have questioned whether there is an increase in survival with ECP monotherapy.

A majority of reports of patients with MF and SS treated with ECP have, however, included the use of adjuvant therapy (Table II),[80-86,88,90,92-96,100-102,153,164] especially interferon alfa, and the RRs have in general been higher with the combination versus monotherapy. A combined analysis of more than 400 patients treated with ECP and adjunctive therapies showed an overall RR for all stages of CTCL of 55.7% (244 of 438) with 17.6% (77 of 438) achieving a CR.[148] Duvic et al[149] reported a 40% OR in patients with stage III to IV MF/SS treated with at least 6 cycles of ECP therapy alone versus 57% OR in those treated in combination with interferon alfa, bexarotene, or granulocyte monocyte colony-stimulating factor. Arulogun et al[155] performed a retrospective review of patients with SS (defined as at least two of the following: >5% SCs, CD4/CD8 ≥10, and/or clonal TCR gene rearrangement) treated with ECP 2 times per week for the first week, weekly × 6 weeks, every 2 weeks for 6 weeks, then monthly in combination with various systemic therapies (steroid, MTX, interferon alfa, bexarotene) in 10 of 13 patients versus 3 of 13 patients treated with monotherapy ECP. There were 7 of 10 responders in those treated with combination therapy versus 1 of 3 treated with ECP alone. There has only been one prospective randomized trial of ECP in combination with interferon alfa-2a versus interferon alone.[47] Twenty patients with MF/SS stages IA to IVB were treated with either ECP two consecutive treatments monthly plus interferon alfa-2a 18 MU qd × 3 months

reduced to 3 MU qd × 9 months (9 patients) versus interferon alone (11 patients): there was RR of 22% (two of 9 PR) on the combination arm versus 36% (4 of 11 with one CR [the lone patient with SS] and 3 PRs) on the interferon alone arm (E. Olsen, MD, unpublished data). The effect of ECP has not appeared to add additional value when given with chemotherapy: there was a PR in 4 of 10 patients with stage IIA to IV (no CR) to a combination of standard ECP plus various chemotherapeutic agents (chlorambucil, MTX, combination chemotherapy, doses and dosing regiments not specified).[153] Whether ECP would be of value after a remission from chemotherapy induction remains to be determined.

ECP is well tolerated with few complications or adverse effects.[148] Uncommon adverse reactions are usually vascular related and include the following: fluid-responsive hypotension, venipuncture-site hematomas, rare exacerbation of congestive heart failure or arrhythmias, superficial thrombophlebitis, catheter-related sepsis, rare herpes infections, and rare disseminated fungal infection.[148-150]

CHEMOTHERAPEUTIC AGENTS
Methotrexate

MTX works by blocking cell division in the S phase. It inhibits dihydrofolate reductase that converts dihydrofolate to tetrahydrofolate, which is required for synthesis of thymidylate and purine nucleotides involved in DNA and RNA synthesis. It also inhibits thymidylate synthetase. In addition, MTX has anti-inflammatory effects. It inhibits methionine synthetase and aminoimidocarboxyamido-ribonucleotide transformylase thereby reducing S-adenyl methionine and increasing adenosine.[165]

The reported RR of low-dose MTX (defined as doses <100 mg/wk) in MF/SS ranges from 9 of 16 "definite improvement" in the first report using 2.5- to 10-mg dose daily[166] to reports by Zackheim et al[167] of RR of 58% (17 of 29) in patients with E-MF to 33% (20 of 60) in patients with plaque-stage MF[168] given median weekly doses of 25 mg. Winkelmann et al[169] did not note a response in the 4 patients with SS he treated with MTX (regimen not specified). The RR to high-dose MTX (60-240 mg/m^2 IV) with leucovorin rescue as reported by McDonald and Bertino,[170] however, is impressive with more than 80% clearing in 9 of 11 patients, the majority with lymphadenopathy, and including 7 of 11 with a CR. An overall RR to single-agent MTX in SS is difficult to estimate because of the small number of well-documented cases reported.[169-171]

There are also studies using MTX in combination with another agent for SS (Table II).[90,172,173] A small study of IV MTX 60 mg/m^2 over a 24-hour infusion

followed by 5-fluorouracil 20 mg/kg over 36 to 48 hours with leucovorin rescue showed at least 80% clearing in both of two patients with SS and one of two patients with E-MF.[172] Another study of low-dose oral MTX 10 mg/m^2 twice weekly and interferon alfa 9 MU SQ tiw was performed among patients with refractory MF/SS. There were 89 of 158 stage III cases (unknown how many were SS vs E-MF) plus 33 of 158 stage IVB, some with T$_4$ skin (probably including SS).[89] All other cases were stage IIB yet overall CR was 74% by 1 year with 10-year survival of 70%. Hirayama et al[173] reported on a single patient with SS who had a durable (>4 year) PR to combination therapy with low-dose MTX 10 mg/wk and etoposide 25 mg/d.

There is a recent study of a MTX-related compound in which 15 MF/SS cases (the majority with large cell transformation) were aggregated and showed a 47% RR to IV trimetrexate (200 mg/m^2 biweekly).[174] Horwitz et al[175] reported on the phase I results of pralatrexate, another antifolate analog, used in 20 to 30 mg/m^2 doses × 2 of 3 weeks or 3 of 4 weeks to treat 11 patients with MF/SS. There was an OR of 45% including two of 11 CR. MRD and specifics regarding patients with SS were not noted.

Potential side effects of MTX include GI (nausea, vomiting, stomatitis, diarrhea, ulcers), bone marrow (leukopenia, anemia, thrombocytopenia), liver (increased transaminases, hepatitis, fibrosis, cirrhosis, the latter two cumulative dose related), lung (pneumonitis, fibrosis), pregnancy (teratogen, abortifacient), and miscellaneous (alopecia, photosensitivity reactivation sunburn, radiation recall, oligospermia, anaphylaxis).[165] MTX-induced lymphoproliferative disorders have been reported including in one patient with SS.[176] Toxicity of MTX can be enhanced by drug interactions with other folate antagonists (trimethoprim, sulfonamides, dapsone), hepatotoxins (ethanol, retinoids), conditions that result in elevated blood levels (reduced renal excretion and displacement from protein binding), or underlying liver disease including metabolic syndrome. Oral folic acid supplementation (1-5 mg daily) combats GI symptoms,[177] although questions have been raised whether dose or dosing of folic acid affects efficacy.[178] Leucovorin (folinic acid) rescue is used to rescue normal tissue, especially that of the kidney, when high-dose MTX is used or to counteract acute toxicity regardless of dose.

Purine analogs (fludarabine monophosphate, 2-chlorodeoxyadenosine, and deoxycoformycin)

Fludarabine. Fludarabine is a fluorinated adenine nucleoside resistant to deamination. On infusion,

it is first dephophosphorylated to 2-fluoroadenine arabinoside triphosphate, which on intracellular diffusion is phosphorylated by deoxycytidine kinase (dCyk).[179] The accumulation of 2-fluoroadenine arabinoside triphosphate curtails DNA synthesis through inhibition of ribonucleotide reductase and DNA polymerase alpha. Fludarabine may be particularly useful in T-cell malignancies because of its apoptotic induction of death of pathogenic T cells.[180] Fludarabine is FDA approved for the treatment of chronic lymphocytic leukemia (CLL).

Reports of fludarabine monotherapy in CTCL are few: those in SS are shown in Table I.[181,182] Redman et al[183] described 5 patients with MF (not otherwise specified) who were treated with 25 mg/m^2 fludarabine × 5 days every 3 to 4 weeks: there were two of 5 responders. Von Hoff et al[184] randomized 33 patients with MF (SS unknown) to treatment with either 25 mg/m^2 (treatment naive group) or 18 mg/m^2 (prior systemic or radiation therapy) of fludarabine daily × 5 days every 28 days. Of the 31 evaluable patients who averaged over 46 courses of treatment, there was a 19% RR including one CR. Quaglino et al[181] treated 27 patients with MF and 17 patients with SS with fludarabine alone at the above dose with a RR of 30% including a CR of 9% in the patients with MF and 35% RR including 18% (3/17) CR in those with SS. Other significant untoward effects of fludarabine are prolonged T-cell dysfunction and the potential to introduce secondary neoplasia.

Combination therapy has yielded only slightly better results (Table II).[79,185] Foss et al[79] treated 35 patients with CTCL—24 with MF and 11 with SS (T$_4$ plus peripheral SCs)—with fludarabine 25 mg/m^2 × 5 days every 28 days along with interferon alfa at 5 to 7.5 MU SQ tiw. CR was seen in 4 of 35 (11%) including 3 of 11 patients with SS and 3 of 4 of the CRs were maintained more than 18 months. Scarisbrick et al[185] treated 8 patients with SS (defined as erythroderma with >10% abnormal circulating lymphocytes and TCR gene rearrangement clone) with fludarabine 18 mg/m^2 and Cytoxan 250 mg/m^2 × 3 days every month for 3 to 6 months. There was a response in 4 of 8 patients with SS including one CR but no clear improvement in survival. Publications using fludarabine in combination with other therapies in the treatment of SS are shown in Table II.

Potential side effects of fludarabine include myelosuppression especially neutropenia and its attendant risk of infection, which is generally moderate and reversible; GI symptoms of nausea, vomiting, and diarrhea; infrequent somnolence and fatigue; prolonged T-cell dysfunction; the potential to induce secondary neoplasia; and uncommon pulmonary toxicity.[179,184] Severe neurotoxicity has been seen

with the use of much higher doses of fludarabine than those used to treat CTCL but has been reported sporadically at lower levels.[186]

2-Chlorodeoxyadenosine (cladribine). 2-Chlorodeoxyadenosine (CDA) is a nucleoside analog that accumulates in the cell as a result of its resistance to adenosine deaminase and its phosphorylation by dCyk to 2-CDA-triphosphate. The high activity of this kinase in lymphocytes ensures accumulation of toxic concentrations of the drug in these cells. It is postulated that 2-CDA-triphosphate inhibits ribonucleotide reductase and DNA polymerase leading to accumulation of deoxynucleotides and DNA strand breaks that interfere with DNA repair and accelerate apoptosis.[187] 2-CDA is available in IV form and approved for the indication of hairy cell leukemia.

2-CDA has shown efficacy in MF and SS with various dosing regimens. O'Brien et al[188] in 1994 reported on one of 8 patients with MF who had a CR with daily infusions of 4 mg/m^2 2-CDA $\times$ 7 days repeated every 28 days. Trautinger et al[189] reported on 8 patients with MF who were treated with low-dose 2-CDA 0.06 mg/kg/d for 5 days every 4 weeks: there was a PR in two of 8 patients but none among those with erythroderma. Kong et al[190] presented the Northwestern experience of 24 patients with MF/SS (80% $\geq$ stage IIB) who were treated with 2-CDA 0.1 mg/kg/d by continuous infusion over 5 to 7 days every 28 days. The RR was 24% with 3 of 24 CR and 3 of 24 PR. OR has been seen in 0% to 50% of the 13 reported patients with SS[191-193]; those patients who have documented T$_4$B$_2$ status are shown in Table I.[191,193]

Side effects of 2-CDA are primarily myelosuppression, especially effecting neutrophils and platelets, and a protracted lymphopenia with a marked decrease in the CD4/CD8 ratio that lasts 6 to 9 months posttreatment.[109] Related to this immunosuppression is a high risk of infection. Neurotoxicity is much less common at lower doses and hepatic or renal toxicity is unusual. Mild nausea and fever may occur.

Deoxycoformycin (pentostatin). Deoxycoformycin (DCF) is a potent inhibitor of adenosine deaminase.[194] DCF blocks the deamination of adenosine to inosine and deoxyadenosine to deoxyinosine, resulting in an accumulation of intracellular deoxyadenosine and deoxyadenosine triphosphate. These metabolites block DNA synthesis through the inhibition of ribonucleotide reductase and are especially toxic to lymphocytes. Deoxyadenosine also inactivates 5-adenylhomocysteine hydrolase in blood cells of DCF-treated patients leading to accumulation of S-adenosylhomocysteine, an inhibitor of many transmethylation reactions.[195] The mean terminal elimination half-life after IV infusion of DCF is 5.7

hours, much longer in those with renal impairment, with ~90% of the drug excreted in the urine.[109] DCF is FDA approved as an IV formulation for the treatment of hairy cell leukemia.

DCF has demonstrated clinical activity in all stages of CTCL. In an early phase I study of 4 patients with plaque and tumor stage, one patient received 4 mg/m^2/d, two received 8 mg/m^2/d, and one received 10 mg/m^2/d of DCF for 3 days repeated every 28 days.[196] Two of the patients (8 mg/m^2) achieved a CR that lasted for 7 to 9 months. The remaining two patients achieved a PR that lasted 4 to 9 months. Three of the 4 patients achieved 100% inhibition of adenosine deaminase. Tsimberidou et al[197] presented the M.D. Anderson Cancer Center (Houston, TX) experience with 32 patients with stage IIB to IV MF/SS who were treated with DCF 5 mg/m^2 $\times$ 3 days every 3 weeks: there was a 31% RR with two of 32 CRs. The Eastern Cooperative Oncology Group presented 4 of 8 patients with CTCL and a global PR to the same dosing regimen, with at least one patient having a response that lasted 1.6 years.[198] Greiner et al[199] treated 18 patients with MF/SS with one of 3 dosing regimens of DCF for a median of 5 courses of treatment: 4 mg/m^2/wk (one patient), 5 mg/m^2 $\times$ 3 days every month (3 patients), or 4 mg/m^2 every week (14 patients). There was an OR rate of 39% with two of 18 CR and 5 of 18 PR and a disease-free survival of 1.5 to 6 months in the patients with PR and 4 and 76 months in the patients with CR.

The response specifically of patients with SS to monotherapy with DCF is given in Table I.[200,201] A phase II EORTC trial of DCF was conducted at 92 centers and included 22 patients with MF and 21 patients with SS.[200] Patients received 4 mg/m^2 of DCF weekly for 3 weeks then every other week for 6 weeks followed by maintenance treatment with 4 mg/m^2 monthly for 6 months. There was a 33% RR in the patients with SS (one CR and 6 PRs) and a 23% RR in the patients with MF (5/22 PR, no CR). A dose-adapted regimen of DCF was explored by Kurzrock et al[202] in 27 patients with CTCL including 14 patients with SS (not otherwise defined) and 6 patients with tumor-stage MF. The starting dose was 5 mg/m^2/d for 3 days every 3 weeks and was increased or decreased by 1.25 mg/m^2/d on subsequent courses based on toxicity. Patients with SS had an overall RR of 71% (4/14 CR, 6/14 PR) whereas the RR in MF was 66% (1/6 CR and 3/6 PR).

A combination study of DCF with intermittent high-dose interferon alfa was conducted in 41 patients with advanced or refractory MF/SS.[78] DCF 4 mg/m^2/d for 3 days every 42 days was given along with interferon at a dose of 10 MU on day 22 and 50 MU on days 23 to 26 for at least two cycles. The

overall RR was 41% with two of 41 CR (both in the patients with SS) and 15 of 41 PR. Patients with erythroderma had a higher RR (8/18 or 44%) than those with tumor-stage disease (3/15 or 20%).

The most common side effects of DCF are hematologic, GI, nonneutropenic fever, and transient elevation of liver function test results.[197-203] Infections, including life-threatening pneumonia and sepsis, have been reported and may occur months after stopping DCF. The latter may be related to the long-term (>1 year) depression of CD4 counts that have been reported.[197] Less common side effects include neurologic problems (confusion, seizures, peripheral neuropathy), pulmonary toxicity especially bronchospasm, mild nephrotoxicity, conjunctivitis/scleritis, and rash.

Gemcitabine (Gemzar)

Gemcitabine is a deoxycytidine analog (2', 2'-difluorodeoxycytidine), a pyrimidine antimetabolite, subgroup of nucleoside analogs, with antitumor cytotoxic activity. On entering cells via nucleoside transporter proteins, it is phosphorylated by dCyk to gemcitabine monophosphates, diphosphates, and triphosphates. These phosphorylated substrates inhibit elongation of DNA chain via "masked chain termination" and competitively inhibits ribonucleotidyl reductase leading to impaired DNA synthesis and induction of apoptosis. Metabolic clearing is by deamination but gemcitabine-triphosphate inhibits deoxymonophosphate deaminase, possibly providing one mechanism for the prolonged retention phenomenon that distinguishes gemcitabine from other pyrimidine analogs.[204] Gemcitabine is approved as an IV infusion for ovarian, breast, nonsmall cell lung, and pancreatic cancer.

Although gemcitabine is widely used in the treatment of patients with MF or SS, there are limited published data of efficacy. In CTCL (MF plus SS), the overall RRs range from 65% to 73%,[205-207] although most are PRs with variable response durations. A brief report by Sallah et al[208] showed a PR in both of two patients with CTCL treated with 1200 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Zinzani et al[206] treated 30 patients with tumor-stage or T_4 MF with 1200 mg/m^2 IV on days 1, 8, and 15 of a 28-day schedule for at least 3 courses: there was a cutaneous RR of 70% including 3 of 30 CR and 18 of 30 PR. The reports that include patients with SS are very limited and are mixed among the reports of other patients with CTCL. Marchi et al[207] treated 26 patients with MF (all tumor-stage or T_4 skin disease) and one patient with SS (criteria not given) with a 73% RR including 6 of 26 CR and 13 of 26 PR in the patients with MF and no response in the patient with SS. Duvic et al[205] treated 20 patients with MF and 11 with SS (the only patients with criteria for SS given in any report) with gemcitabine 1000 mg/m^2 IV on days 1, 8, and 15 monthly for at least 6 cycles for an overall RR of 65%: this included 3 CR and 9 PR in 20 patients with MF and 8 PR in 11 patients with SS.

Overall, gemcitabine was well tolerated in all reports. Hematologic toxicities, including neutropenia, thrombocytopenia, and anemia, were observed in 20% to 60% of patients: they were mostly grade 1 to 2 with rare grade 3 to 4 events. Dose reduction was routine with grade 3 to 4 hematologic toxicities. Nonhematologic toxicities included fever (flu-like), nausea/vomiting, interstitial pneumonitis (mild to severe dyspnea), transient increases of liver function test results (occasional grade 3), rare renal symptoms including hemolytic uremic syndrome, thromboses, rare arrhythmias, left ventricle dysfunction, erythema flare response, diffuse hyperpigmentation in SS, alopecia (mild-moderate), radiation sensitivity, and recall. Specific to patients with SS, two cases of hemolytic uremic syndrome and several patients with cutaneous erythema flare and hyperpigmentation were reported by Duvic et al.[205]

Forodesine

Forodesine hydrochloride (BCX-1777, BioCryst Pharmaceuticals, Birmingham, AL) is a rationally designed small-molecule, transition-state analog inhibitor of purine nucleoside phosphorylase (PNP).[209] Under normal physiologic conditions, deoxyguanosine undergoes phosphorolysis by PNP to guanine and ribose 1-phosphate.[210] When PNP is inhibited in lymphocytes, dCyk shunts unmetabolized deoxyguanosine into deoxyguanosine triphosphate that accumulates, inhibits the conversion of ribonucleoside diphosphates to deoxyribonucleoside diphosphates, which in turn, inhibits DNA synthesis and cell replication and leads to apoptosis.[210,211] Although PNP is present in all mammalian cells, human T cells are especially susceptible to the deficiency of this enzyme because they selectively have high dCyk activity and/or low nucleotidase activity.[212] Forodesine has been shown to inhibit the proliferation of activated human T lymphocytes and acute lymphoblastic leukemic T cells in vivo and in vitro.[210,212,213] Forodesine is currently in phase III clinical trials for the treatment of MF/SS.

In a phase I, open-label, multicenter, IV dose-ranging study of 40, 60, 90, and 135 mg/m^2 every 12 hours in 9 doses over 4.5 days repeated at 2-week intervals,[214,215] 4 of 13 patients with MF/SS (31%) had an OR and 9 of 13 had either improvement in erythroderma or decrease in the SS cell count or the CD4:CD8 ratio. The activity and bioavailability of

oral forodesine was also demonstrated in a multi-center dose-escalation phase I trial of 40, 80, 160, or 320 mg/m^2 oral forodesine daily for 4 weeks in patients with stage IB or higher MF/SS.[215] There were PRs in 3 of 14 patients, all in the 80-mg/m^2 cohort. No dose-limiting toxicities were observed with the target dose of 320 mg/m^2 but based on pharmacokinetics (PK)/pharmacodynamics results, the 80-mg/m^2 dose was identified as optimal.[215] A phase II trial with 30 patients with MF/SS treated with 80 mg/m^2 rounded to the nearest 100-mg capsule (essentially a fixed oral dose of 200 mg/d forodesine) was then undertaken with two CRs and 9 PRs for a 37% RR.[215,216]

Forodesine is well tolerated in most patients. The most common side effects are fatigue, peripheral edema, nausea, pruritus, dyspnea, and headache. Grade 3 to 4 lymphopenia has occurred in 70% of patients and low CD4 counts in 32% of patients in the phase II oral clinical trial.[216] There is little effect on hemoglobin, neutrophils, or platelets. Opportunistic infections are uncommon.

Alkylating agents

Chlorambucil (Leukeran). Chlorambucil (Leukeran) is a bifunctional alkylating agent first synthesized by Everett et al[217] in 1953 based on modification of the parent nitrogen mustard structure. Alkylation of DNA results in strand breaks and interstrand cross-linking, disrupting DNA replication and RNA transcription. It is a cell cycle phase nonspecific antitumor agent. Chlorambucil is available in tablet form and orally administered, where it is rapidly and virtually completely absorbed from the GI tract. Peak plasma levels are observed within 1 hour. The terminal elimination half-life is approximately 1.5 hours, and it is efficiently metabolized to phenylacetic acid mustard with limited urinary excretion. The parent agent and metabolites degrade spontaneously in vivo to the inactive monohydroxy and dihydroxy derivatives. Chlorambucil is highly bound to albumin and there are no known drug-drug interactions with chlorambucil.[217,218]

With the early recognition of the use of nitrogen mustard and derivatives, especially chlorambucil, in managing leukemias and lymphomas, studies to evaluate the effect of chlorambucil in MF and SS were performed. Libansky and Trapl[219] first reported success in treating 4 patients with "erythrodermia" (clinical and laboratory evidence for SS) with chlorambucil in doses of 4.6 to 5.6 mg/kg for 4-week cycles. Marked clinical responses were observed with remissions from 4 to 24 months. They also reported the initial treatment of a case of MF refractory to multiple previous therapies with

excellent response to chlorambucil. Several case reports have shown variable activity of chlorambucil as a single-agent therapy in treatment of MF. Wright et al[166] examined chlorambucil 2 to 28 mg/d (average 10 mg) in 9 patients (6 evaluable) with MF with some transient responses but no OR. Only 3 other reports have suggested some benefit using chlorambucil for MF: one case report with monotherapy, and 6 cases with chlorambucil and prednisone.[220-222]

More extensive trials have been conducted for SS using chlorambucil (Table I).[97,223,224] In all these studies, oral corticosteroid has also been used in conjunction with chlorambucil to maintain responses and duration of improvement. In these open trials, all patients had skin and blood involvement and some had clinical evidence of nodal disease as well. Continuous treatment with chlorambucil (2-6 mg/d) in conjunction with prednisone (initially ∼20 mg/d, tapering over time) (regimen of Winkelmann et al[169,224]) resulted in a significant response in patients with SS.[223] In the study reported by McEvoy et al,[225] leukapheresis was also performed concurrently with an OR of 100% including two of 11 CR. MRD was 1 to 3 years and mean time to death was 6.5 to 8 years versus historical controls of 3 years. Coors and von den Driesch[97] reported their clinical experience with pulse chlorambucil and fluocortolone in patients with stage III to IVb treated with chlorambucil 10 to 12 mg/d and fluocortolone 75-50-25 mg on 3 successive days every 2 weeks. Of 13 patients, 7 (54%) achieved CR and 6 (46%) achieved PR. MRD was 16.5 months. Publications using chlorambucil in combination with other therapies in the treatment of SS are shown in Table II.[97,225]

Low-dose chlorambucil is generally well tolerated with few significant side effects. The main toxicity is leukopenia, which should be monitored by monthly complete blood cell counts. The effectiveness of the therapy for SS is likely partly a result of this side effect. Myelosuppression, immunosuppression, drug fever, and hyperuricemia are early side effects and delayed side effects include amenorrhea, azoospermia, infertility, pulmonary interstitial fibrosis, cystitis, hepatotoxicity, peripheral neuropathy, and the late effects of acute leukemias and solid tumors that are seen with other alkylating therapies. Chlorambucil is teratogenic and should not be used in pregnancy.[218]

Nitrogen mustard (Mustargen). Karnofsky[226] in 1950 reported on 21 cases of MF treated with nitrogen mustard 0.1 mg/kg/d × 10 days: there was a rapid and marked response to the first cycle that lasted 5 to 7 months. Subsequent treatments were

less effective. Because of the efficacy shown with topical nitrogen mustard, Van Scott et al[227] in 1975 examined the use of systemic nitrogen mustard again in 27 patients with plaque-stage MF and 14 with E-MF/SS including 6 with peripheral blood SC counts greater than or equal to 20% (here termed "SS") (Table I). They used various regimens including nitrogen mustard by IV push 0.5 to 3 mg daily, 1 to 3 mg tiw, 1 to 1.5 mg twice a day, or a 6- to 8-hour IV infusion of 2 mg daily with a total amount of nitrogen mustard per course equal to ~0.4/mg/kg. Importantly, all patients were also treated with concomitant topical nitrogen mustard. An OR was seen in 57% of the 14 patients with erythroderma, including 6 of 11 of those with nodal disease and 4 of 6 of those with SS (T_4 plus SCs >20%) including at least one response lasting more than a year.

IV Mustargen may cause thrombosis or thrombophlebitis, myelosuppression with an acute effect on lymphocytes, rash, and GI symptoms. It is a probable carcinogen and mutagen.

Cyclophosphamide (Cytoxan). Cyclophosphamide is an alkylating agent, a phosphamide ester of mechlorethamine that induces intrastrand cross-links during cell division requiring excision repair.[218]

The first report of cyclophosphamide in the treatment of MF was by Abele and Dobson[228] in 1960. Four patients with biopsy-proven MF (two with exfoliative dermatitis that would probably be qualified as erythroderma today, one with widespread dermatitis and one with plaque disease) were treated with 200 mg of IV cyclophosphamide × 14 to 20 days with an OR at the end of induction in all patients and clearing of skin in 3 of 4 patients including the two with erythroderma. Maintenance cyclophosphamide therapy was necessary to maintain the response and the optimum dosing appeared to be single weekly dosing of 400 to 700 mg. Van Scott et al[229] reported on 10 patients with MF, all tumor or plaque stage, treated with varying doses of 50 to 175 mg IV cyclophosphamide until leukopenia or thrombocytopenia developed at which point drug was stopped and restarted on recovery. With this dosing regimen, there was a skin PR in two of 10 and CR in two of 10. Mendelson et al[230] reported on a patient with MF who failed to respond to 8 courses of 1500 mg/m² cyclophosphamide given approximately every 3 weeks. Three other case reports of plaque- and tumor-stage MF responding to 100 to 200 mg/d of cyclophosphamide have been noted.[231-233] In general, cyclophosphamide has been used much more frequently as part of a multiagent chemotherapy regimen, including in SS, versus monotherapy.

With the exception of the lower (400-700 mg weekly) maintenance regimen of Abele and Dobson,[228] in which the main side effects seen in 4 patients treated for 2 to 12 months were alopecia, nausea, and vomiting with no leukopenia or thrombocytopenia, leukopenia[229] has been the dose-limiting factor for continuous dosing. The potential for hemorrhagic cystitis with oral dosing and, in young patients, germ cell damage, remain as concerns.

Temozolomide (Temodar). Temozolomide, an imidazotetrazine derivative, is an oral alkylating agent approved for the treatment of glioblastoma multiforme and anaplastic astrocytoma. Temozolomide functions as a prodrug, undergoing rapid nonenzymatic conversion to active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide.[109] Its cytotoxicity is thought to be a result of alkylation (methylation) of DNA mainly at the 0^6 and N^7 positions of guanine with depletion of the DNA repair protein 0^6-alkylguanine-DNA alkyl transferase.[109,234] Food decreases absorption and temozolomide is rapidly eliminated with an elimination half-life of 1.8 hours.[109]

There have been two studies evaluating the efficacy of temozolomide in MF. Temozolomide was evaluated in a phase I study of 42 patients with a variety of types of advanced cancer in doses of 750, 900, 1000, and 1200 mg/m² × 5 days in a 4-week cycle.[235] One patient with MF had a CR in the skin of 7 months' duration. A prospective single-center phase II study of temozolomide 150 mg/m²/d × 5 days on first 28-day cycle then 200 mg/m² × 5 days on cycles 2 and 3[236] was conducted in 9 patients with MF stage IIB or III. There was an OR in 33% of patients including one CR and two PRs with a duration of response of 6 to 9 or more months. There is no mention of results in SS specifically in either report.

Temozolomide is well tolerated. Myelosuppression (leukopenia, thrombocytopenia) is the dose-limiting side effect with a predictable nadir at day 22 and mild nausea and vomiting is reported.[234] Infection is uncommon.

Topoisomerase inhibitors
VP-16 (etoposide). VP-16 is a semisynthetic derivative of the plant toxin podophyllotoxin used first line for the treatment of small cell lung cancer. It is also used for testicular tumors and as combination therapy for a variety of hematologic malignancies. It is available in an IV and oral formulation.[237,238] Although it induces single-strand and double-stranded DNA breaks, its major mechanism of action appears to be through reversibly binding to DNA topoisomerase II, resulting in the inability of this enzyme to repair double-stranded DNA breaks. Interference with this enzyme results in disrupted

transcription and, ultimately, cytotoxicity and cell death. Of the IV dose of VP-16, 30% to 40% is recovered in the urine unchanged with the remainder metabolized primarily to glucuronide or hydroxy acid forms. The terminal half-life is ~5.6 hours with clearance correlated with creatinine clearance. Oral dosing is subject to variable absorption with no effect from food but decreased absorption with increased dose.

The first reports on the use of VP-16 for CTCL were in 1975. One patient with tumor-stage MF had a CR to VP-16 60 mg/m^2 IV $\times$ 5 days repeated every 2 weeks with maintenance biw injections.[239] A second case of a patient with a generalized dermatosis compatible histologically with MF was treated with 60 mg/m^2 VP-16 $\times$ 5 days every 2 weeks $\times$ 5 courses with a CR maintained for greater than 1 year on maintenance 60 mg/m^2 $\times$ 5 days followed by 100 mg/m^2 biw of the remaining 3 weeks of the 4-week cycle.[240] Onozuka et al[241] reported on a patient with E-MF without blood involvement who was treated initially with IV weekly 150 mg/d VP-16 and oral prednisolone $\times$ 3 d/wk for 9 weeks followed by oral VP-16 (25 mg/d $\times$ 21 days every 4 weeks) with a CR of 36 months. Nasuhara et al[242] reported on a patient with non-E-MF and histologically confirmed pulmonary involvement who had a 36-month remission when treated with weekly oral VP-16 (200 mg) and prednisolone (30 mg) thrice weekly. The Scandinavian Mycosis Fungoides Group treated a total of 9 patients with MF (SS included but not defined or otherwise identified in results) with VP-16 alone 100 mg IV $\times$ 5 days every 2 to 3 weeks and oral VP-16 100 mg qd $\times$ 5 days during maintenance every 2 to 3 weeks or in combination with cyclophosphamide 500 mg IV every fourth day during induction and 150 mg qd orally during maintenance.[243] Of the 5 patients with MF (3 skin only, two with nodal involvement) treated with single-agent VP-16, there was one CR and one PR. In the 4 patients treated with cyclophosphamide in combination with VP-16, there were two CR and one PR. Progressive disease generally occurred 4 to 6 months after the start of therapy.

There has only been one case report using VP-16 as monotherapy in patients with SS. Miyoshi and Noda[244] reported a PR that persisted for 48 months but did not define the criteria used for SS diagnosis nor the dose of VP-16 used. Olsen and Lai reported on the use of 50 to 100 mg oral VP-16 $\times$ 20 days every month in 4 patients with SS (erythroderma, lymphadenopathy, diffuse pruritus, and >15% SC): there was a PR in one of 4 patients that lasted 6 months while on therapy (E. Olsen, MD, and E. Lai, BS, unpublished data). Hirayama et al[173] reported on the

use of VP-16 25 mg/d orally in combination with MTX 10 mg every week in a patient with SS: there was a reduction in the leukocyte count and adenopathy and resolution of erythroderma. Publications using etoposide in combination with other therapies to treat SS are shown in Table II.

VP-16 is generally well tolerated. Serious side effects are primarily hematologic (reversible myelosuppression) and are often dose limiting. Other potential side effects include GI (nausea, vomiting), mucositis, alopecia (total), and rarely hypersensitivity reactions. Increased toxicity has been seen with impaired renal function and decreased albumin presumably secondary to increased exposure to unbound VP-16.[238] Chronic VP-16, especially weekly or biweekly dosing, has been associated with acute myeloid leukemia.[245] Potential advantages for the use of VP-16 include that it is available in an oral formulation, it can be given on a chronic dosing schedule, and its safety in the elderly has been established.[237,238]

Pegylated liposomal doxorubicin (Doxil). Doxorubicin HCl is an anthracycline topoisomerase inhibitor approved for the treatment of ovarian cancer, multiple myeloma, and Kaposi sarcoma with activity also in non-Hodgkin lymphoma. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Pegylated liposomal doxorubicin is a formulation of doxorubicin encapsulated in liposomes, microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The size of the liposomes allows selective accumulation in the tumor vascular bed and the surface-bound methoxy polyethylene glycol (pegylation) induces reduced clearance by the mononuclear phagocyte system thereby improving the PK and pharmacodynamics. Once the liposomes distribute to the tissue compartment, the encapsulated doxorubicin HCl is released.

Adriamycin has previously shown efficacy as monotherapy in advanced MF/SS[246] and has been an effective agent in multiple combination chemotherapy regimens as well. Although Doxil is used increasingly in the treatment of patients with MF or SS, the published data to support its use in SS are limited. In CTCL (MF + SS), the overall RR has ranged from 30% to 80% with CR rates of 20% to 60%.[247-249] In a report of 31 patients with MF/SS, Wollina et al[247] used various dosing regimens of liposomal doxorubicin of 20 or 30 mg/m^2 every 2 to 4 weeks (in most cases) and 40 mg/m^2 (two patients). There was a particularly high RR of 87% including 12 of 30 CR and 14 of 30 PR that may have been partly related to the definition of PR used (either >50% decrease in the size of lesions or >50% change of nodular or plaque

lesions to macular ones) along with the use of interferon alfa in two patients. However, Pulini et al,[248] in a study of 19 patients with CTCL (13 with MF, 3 with peripheral T-cell lymphoma, and 3 with SS) treated with liposomal doxorubicin 20 mg/m^2 IV every 4 weeks and using a global response criteria, reported a RR of 84% including CRs in 50% of the patients with MF/SS (7 of 13 MF and one of 3 SS). Quereux et al,[249] using similar dosing, reported a RR of 56% in 25 patients with MF/SS including 20% CRs: there was CR in 4 of 15 patients with MF and one of 10 with SS, and PR in 4 of 15 patients with MF and 5 of 10 with SS. In a study by Di Lorenzo et al[250] that was restricted to 10 patients with stage IVB MF (SS not defined) who were treated with 20 mg/m^2 every 8 weeks, 30% (all heavily pretreated) achieved a PR.

Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m^2 or at lower cumulative doses (400 mg/m^2) in patients who are receiving concurrent cyclophosphamide therapy. Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with liposomal doxorubicin. Severe myelosuppression may occur and liposomal doxorubicin may potentiate the hematologic toxicities of other chemotherapeutic agents. Hand-foot syndrome may occur during therapy with Doxil, generally after 2 to 3 cycles of treatment, and may require dose reduction, delay in administration, or discontinuation of Doxil. Other potential side effects include radiation recall, mucositis, alopecia, asthenia, fatigue, and GI symptoms. Liposomal doxorubicin is eliminated in large part by the liver and it is recommended that dosage be reduced in patients with impaired hepatic function. Fortunately, the toxicity profile in the CTCL experience of approximately 88 patients treated across several studies has been excellent and most events reported have been grade 1 or 2 in less than 20% of patients.[247-250] Grade 3 to 4 toxicities have been rare and have included anemia, neutropenia, lymphopenia, hand-foot syndrome, and capillary leak syndrome.

HISTONE DEACETYLASE INHIBITORS

Histone deacetylase (HDAC) inhibitors are compounds that target the epigenome and cause pleiotropic effects including tumor cell-selective apoptosis. There is increasing evidence of epigenetic abnormalities in the pathogenesis of CTCL. Increased acetylation of histone and nonhistone proteins by HDAC inhibitors results in transcriptionally active chromatin that alters gene expression and affects protein function, thus, leading to growth inhibition, apoptosis, and cellular differentiation among other antitumor effects.[251]

Vorinostat (Zolinza)

Vorinostat (suberoylanilide hydroxamic acid) is a pan HDAC inhibitor of HDACs in class I (HDAC1, HDAC2, and HDAC3) and II (HDAC6).[109] Vorinostat is orally bioavailable with a mean terminal half-life of 2 hours. In vitro studies have demonstrated that vorinostat selectively induces apoptosis of malignant T cells.[252]

Vorinostat was FDA approved for the treatment of the cutaneous manifestations of CTCL based on two phase II clinical trials. The first was a single-center, dose-ranging study of 33 patients with CTCL with an overall RR of 24% (8 of 33 patients).[253] An optimal dose of 400 mg daily was identified based on response and dose-limiting toxicity of thrombocytopenia at 300 mg twice a day × 2 weeks. Four (36.4%) of the 11 patients with SS had clinical responses. One patient with a circulating SS count of more than 100,000 cells at baseline had a rapid decrease in the absolute SS count to less than 1000 after receiving 300 mg twice daily for 2 weeks but developed thrombocytopenia. The pivotal trial was a multicenter single-arm phase II trial enrolling 74 patients with MF/SS at a fixed dose of 400 mg per day given orally.[41] The overall RR (based on ≥50% reduction in modified severity-weight assessment tool score) was 30% (22/74) and among patients classified as having SS (T$_4$B$_2$), 10 of 30 (33%) were responders. Publications using vorinostat in combination with other therapies in SS are shown in Table II.[102]

The most common drug-related side effects seen during the clinical trials were fatigue, GI symptoms (nausea, vomiting, diarrhea, and the potential for secondary dehydration), hematologic (especially thrombocytopenia and anemia), dysgeusia, anorexia, weight loss, and muscle spasms.[41,253] Alopecia, headache, edema, hyperglycemia, hypophosphatemia, hypomagnesemia, increase in serum creatinine, and corrected QT interval prolongation were reported but generally without sequelae. Prolongation of prothrombin time and international normalized ratio (INR) in patients on coumarin-derived anticoagulants require close monitoring. Thromboembolism was seen in 5% of patients. Infection was uncommon.

Romidepsin

Romidepsin is a potent pan-HDAC inhibitor of the cyclic peptide structural group.[254] It has the greatest activity against selective HDACs in classes I (HDAC1,

HDAC2, and HDAC8), II (HDAC4, HDAC5, and HDAC6), and IV (HDAC 11).[255] It is currently unknown which isoenzyme(s) may be associated with the antitumor effects of romidepsin. Romidepsin has potent in vitro growth inhibitory action as demonstrated in HUT78 cells (CTCL cell line) with the half-maximal inhibitory concentration IC_{50} in the nanomolar range. Romidepsin was approved in 2009 for the treatment of CTCL in patients who have received at least one prior systemic therapy.

Two major independent, international, multicenter phase II single-arm clinical trials of romidepsin in MF/SS were completed: the pivotal study, GPI-04-0001, and the National Cancer Institute (NCI) 1312 study. The data from these two studies are available for further analysis to assess its efficacy in SS.[256,257] Although the two studies are not identical in their enrollment criteria or efficacy assessment tool, both used the same dose and schedule of romidepsin (14 mg/m² in a 4-hour infusion on days 1, 8, and 15 every 28 days). Both studies used a global scoring method where skin and extracutaneous sites of involvement were combined in the assessment of response with the following important differences: in the GPI-04-0001 phase IIB international, multicenter, registration/pivotal study, a PR was defined as greater than 50% improvement in the sum of the 3 assessments (change in skin + change in lymph node + change in peripheral blood Sézary) but with at least 30% improvement in the skin involvement (as determined by severity-weight assessment tool score or in the case of erythroderma, by 5-point erythroderma score), no new tumors (in skin or otherwise), and no worsening of nodes or blood involvement. In the NCI 1312 phase II investigator-initiated study, PR was defined as ≥50% improvement in skin (as measured by PGA tool[110]) without new tumors and no worsening of nodes (blood involvement not considered here). Radiotherapy of nonresponding lesions was allowed in the NCI study, but these lesions were not included in the response assessment. Results in the intention-to-treat population of patients are remarkably similar between studies. In the GPI-04-0001 study of 96 patients with MF/SS (29.2% stage IB-IIA and 70.8% ≥ stage IIB), results included an overall RR of 34.4% (33/96) including 6.3% CR (6/96), median time to response of 1.9 months, MRD of 14.9 months, and median time to progression of 8.3 months.[255] In the NCI study of 71 patients with MF/SS (12.7% stage IA-IIA and 87.3% stage ≥IIB), results included an overall RR of 34% (24/71) including 7% CR (4/71), median time to response of 2 months (1-6), MRD of 13.7 months, and median time to progression of 15.1 months in patients with

an OR and 5.9 months in patients with SD[256] (overall median time to progression of 6.5 months).[255] There were 13 treated subjects in the GPI-04-0001 study who met the criteria of SS (defined as erythroderma plus either ISCL definition of B_2 or >20% SCs) with a RR of 30.8% (4 of 13).[257] Data for the treated SS subjects in the GPI-04-0001 study are presented in Table I.

Overall, romidepsin was well tolerated in both studies. Although asymptomatic T-wave flattening was common in the NCI study,[256] the results of an intensive safety analysis revealed no clinically significant corrected QT interval prolongation or electrocardiogram abnormalities that were attributable to romidepsin. However, concomitant medications that prolong the QT interval or inhibit CYP3A4 are to be avoided with romidepsin. The most commonly reported drug-related adverse events (>20%) in both studies include nausea, fatigue, vomiting, and anorexia.[255] Infection was reported in more than 45% of cases in both studies, however, most of these were attributable to disease and not related to romidepsin. Drug-related adverse events that occurred in both studies in 10% to 20% of patients included diarrhea, headache, dysgeusia, thrombocytopenia, and anemia. Most of these related adverse events were grade 1 to 2 and were very manageable. Lymphopenia and granulocytopenia, regardless of causality, occurred in 3% and 8% versus 55% and 52% of patients in the GPI-04-0001 versus NCI studies, respectively.[255] In all, 55% of patients with the NCI study were hospitalized for at least the first cycle, thus more laboratory assessments were done and all abnormalities were reported regardless of clinical significance, which may account for the differences in the hematologic adverse event profiles. Twelve deaths within 30 days of study administration were reported for both studies together, 3 possibly related to treatment (acute cardiovascular insufficiency after pneumonia; sudden death in setting preexisting valvular disease and cardiomyopathy; and *Escherichia coli* sepsis).[255]

MONOCLONAL ANTIBODIES
Alemtuzumab (Campath)

Campath (alemtuzumab [United States], MabCampath [European Union]) is a humanized IgG1 kappa mAb directed against the human CD52 antigen that is FDA approved for the treatment of patients with CLL.[258] CD52 is a 21- to 28-kd glycosylphosphatidylinositol-anchored glycoprotein whose function is unknown.[259] CD52 is abundantly expressed on mature malignant B and T lymphocytes, monocytes, DCs, eosinophils, NK cells, a subset of granulocytes and epithelial cells of the epididymis,

deferens duct and seminal vesicle; hematopoietic stem cells, plasma cells, erythrocytes and platelets appear to be spared.[259-263] In vitro evidence shows that alemtuzumab induces complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and direct apoptosis in B-CLL cells.[259,262,264] $CD4^+$ cells have about two times the amount of surface CD52 compared with $CD8^+$ cells. The amount of surface CD52 determines not only the type of cytotoxicity (complement-dependent cytotoxicity in $CD4^+$ cells, antibody-dependent cellular cytotoxicity in $CD8^+$ cells) but correlates with the overall sensitivity to killing by alemtuzumab and is inversely proportional to the rate of re-emergence posttreatment: $CD8^+$ cells are effected less than $CD4^+$ cells and return to 25% of baseline after 24 versus 52 weeks off therapy with $CD4^+$ cells.[265] The effect of alemtuzumab on T cells may be through a combination of activation of Tregs and lymphocyte depletion.[262] The biodistribution and clearance of alemtuzumab during treatment is dominated by the tumor burden and does not fit into any simple PK model.[262] Alemtuzumab may be dosed SQ with better tolerability, similar peak drug concentrations achieved but at a higher cumulative dose, and with a greater potential for the development of anti-alemtuzumab antibodies compared with IV dosing.[266]

Unlike most of the other therapeutic options for SS, a relatively large number of patients with SS have been treated with alemtuzumab, many in studies of advanced MF/SS and several in studies of exclusively SS. Gibbs et al[267] successfully treated a patient with simultaneous SS and B-CLL with alemtuzumab 30 mg IV tiw. Using the same dosing regimen, Capalbo et al[268] treated one patient with IVA MF and two patients with E-MF with improvement in all and a CR in one of the patients with E-MF. Kennedy et al[269] treated 6 patients with stage IIB to IV MF and two patients with SS (no information on blood criteria other than presence of circulating SCs) with 30 mg IV tiw × 12 weeks with OR in one of 6 of the patients with MF and both of the two patients with SS. Lundin et al[270] conducted a phase II study of alemtuzumab in 22 patients with heavily pretreated, $CD52^+$, advanced-stage MF/SS (10 patients with T_4 disease and 7 with circulating SCs but unclear how many SS) with 30 mg alemtuzumab IV tiw for up to 12 weeks. RR was 55% (32% CR, 23% PR) and median time to treatment failure was 12 months (5-≥32 months). Lenihan et al[271] treated 8 patients, 3 with MF and 5 with SS (criteria for SS not given), with 30 mg alemtuzumab IV tiw × 12 weeks with a PR in 3 patients (37.5%), all designated SS. Zinzani et al[272] used a lower dose of alemtuzumab 10 mg

tiw IV along with betamethasone each infusion for 4 weeks in 4 patients with MF and tumor or erythrodermic disease: a PR was seen in 3 of 4 patients with no grade 3 or 4 hematologic toxicity.

The results in studies where SS is clearly defined along lines of the ISCL criteria and where all or the majority of patients are SS have shown an impressive overall RR of 86% to 100% with a CR of 21% to 100% (Table I).[42,269,271-275] Of particular note is the lower dosage of alemtuzumab used in 14 patients with SS, and lower incidence of side effects, reported by Bernengo et al.[42] They used a low dose (maximum 10-15 mg) of alemtuzumab delivered SQ and a dosing schedule that was individually determined based on the patient's SC counts. The overall response (skin, node, and blood) was 86% including 3 CRs, median reduction of 96% of SC count, and median time to treatment failure was 12 months. In addition, none of the patients given a maximum of 10 mg alemtuzumab developed hematologic toxicity or infections. Weder et al[276] has proven that alemtuzumab may be successfully used in combination with chemotherapy. A patient with treatment-refractory tumor-stage MF (including failure to respond to gemcitabine and alemtuzumab monotherapies) had a PR on combination therapy with alemtuzumab 30 mg SQ tiw and gemcitabine 1000 mg/m^2 every week and progression-free survival of more than 1 year off therapy. Porcu et al[277] showed that alemtuzumab may be safely administered with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and growth factor support.

Infectious complications are the main concern with alemtuzumab with the frequency depending on the dose and dosing regimen: they are markedly reduced with the 10- versus 30-mg tiw dose and with SQ dosing.[42,272,273] The most frequent observed opportunistic infection is cytomegalovirus reactivation but herpes zoster, generalized herpes simplex, and opportunistic fungal and bacterial diseases have also been reported. Myelosuppression is common with thrombocytopenia, usually noted during the first 2 weeks, neutropenia weeks 5 to 6, and lymphopenia nadir weeks 3 to 6 with recovery of the latter delayed for greater than a year postdosing.[262] Infusional reactions secondary to cytokine release are the most common adverse events during alemtuzumab therapy, particularly IV dosing, and tend to dissipate over time.[262] The dose of alemtuzumab is generally escalated to help minimize this, beginning at 3 mg on day 1 and 10 mg on day 3, regardless of target dose. Local reactions may be seen with SQ dosing. A variety of cardiovascular adverse events were observed in one study but a causative relationship with alemtuzumab has been disputed.[278]

BORTEZOMIB (VELCADE)

26S proteasome is a multicatalytic protease that is responsible for most nonlysosomal intracellular protein degradation and as such, maintains the appropriate balance of cell survival and apoptosis.[279,280] Bortezomib is a cell-permeable dipeptide boronic acid that can reversibly inhibit the chymotryptic-like proteolytic activity of the β_5 subunit of the proteasome.[280] It is FDA approved as an IV treatment for multiple myeloma and mantle cell lymphoma. Bortezomib has an elimination half-life of 9 to 15 hours and it is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and IA2.[109]

Reports of bortezomib in CTCL are limited to one study of 10 patients with previously treated MF (no SS noted).[281] There was a 70% OR rate to bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 every 21 days for 6 cycles: the one CR lasted more than 12 months.

The most common dose-limiting side effects with bortezomib are myelosuppressive (neutropenia and thrombocytopenia).[109,281] Other side effects seen commonly in the myeloma trials were asthenia, GI symptoms, and headache. Sensory neuropathy occurred in 36% of the patients with myeloma and 50% of the patients with CTCL treated with bortezomib with most patients having improvement or resolution off drug. Infection is uncommon.

ANTITHYMOCYTE GLOBULIN (THYMOGLOBULIN)

Antithymocyte globulin (ATG) is commercially available as a purified gamma immune globulin obtained by immunization of rabbits with human thymocytes and is available for IV infusion. Mechanism of action in T-cell malignancies is likely through T-cell clearance from the circulation and modulation of T-cell activation, homing, and cytotoxic activities.[109]

Two case reports of ATG 15 mg/kg in SS have been published and do not appear to support the use of ATG in SS.[282,283] The combination of ATG preceded by cyclophosphamide to induce tolerance to ATG produced only transient improvement.[284]

Potential side effects of ATG include infusion–associated reactions with flu-like illness, GI symptoms, changes in blood pressure, rash and headache, serious immune-mediated reactions including anaphylaxis and cytokine release syndrome (both of which can lead to cardiorespiratory arrest), and serum sickness. Leukopenia, particularly T cells but also neutropenia, and thrombocytopenia may occur.[109]

IL-2 (ALDESLEUKIN/PROLEUKIN)

IL-2 is a 15-kd polypeptide produced by activated CD4$^+$ cells (Th1 cells specifically) that results in activation, proliferation, and maintenance of T helper lymphocytes.[285] IL-2 is also associated with release of IFN-α, TNF-alfa, TNF-B, IL-1, IL-5, and IL-6. It has been shown to be effective in the treatment of a variety of cancers and is FDA approved currently for the treatment of metastatic renal cell carcinoma or metastatic melanoma.

There have been few studies of IL-2 in MF/SS. Nagatani et al[286] treated a patient with tumor-stage MF with IL-2 with a CR for 13 months on monthly dosing. Marolleau et al[287] treated 3 patients with MF and 3 patients with SS (criteria not given) with IL-2 20 MU/m^2 IV on days 1 to 5, 14 to 17, and 28 to 30 and then 1 month later, the same dose 2 d/mo for 5 months. All 3 of the patients with MF had a CR and one of 3 of the patients with SS had a PR. Two of the CRs have lasted for more than 56 and more than 62 months at last report but the PR lasted only 5 months. Gisselbrecht et al[288] used the same induction dose of IL-2 and 20 MU/m^2 × 5 d/mo in 6 patients with MF and one with SS (T$_4$, 30% peripheral blood SC) with a 71% RR including one CR in an patient with MF that lasted longer than 29 months. Gold et al[289] reported on the initial results of 0.5 to 4 MU/m^2/d SQ × 5 days for 4 weeks in a phase I trial of 4 patients with MF stage IIB to IV with two of 4 PR in the skin, one whose adenopathy, however, increased during therapy. Querfeld et al[290] reported on the use of IL-2 at a dose of 11 MU on 4 consecutive days per week for 6 weeks in 22 patients with advanced CTCL: there was an 18% RR.

Side effects of IL-2 have included flu-like illness, GI symptoms, weight gain, increased creatinine, hypotension, cardiac toxicity, vascular leak syndrome, anemia, and thrombocytopenia.[288]

MULTIAGENT CHEMOTHERAPY

Multiple variations of combination chemotherapy have been tried in advanced-stage MF/SS but, despite high initial RRs, responses have generally been short-lived and without documented effect on survival.[185,291-294] Unlike immunomodulators, these chemotherapeutic regimens cannot be sustained long term because of their side effects. Moreover, given the life-threatening toxicities, which result in hospitalizations in many cases, and long-term sequelae of many combination chemotherapy regimens used even for relatively short periods of time, this approach may have a negative impact on the quality of life for many patients so treated. However, because patients with a very high blood tumor

burden are unlikely to respond to immunomodulators alone and/or may urgently need a reprieve from severe symptoms leading to secondary complications in less time than a treatment with immunomodulators or single-agent chemotherapy is likely to deliver, multiagent chemotherapy has its place in the treatment of advanced MF and SS.

It is difficult to sort out the efficacy of the various combination chemotherapy regimens specifically in patients with E-MF or in SS given the small number of reports where their inclusion or response is specifically noted. However, review of the literature illuminates some combination chemotherapies or multimodality regimens that warrant further exploration in MF/SS. For SS, it may be fruitful to focus on those combinations that are able to achieve a near 100% RR including a high (>50%) CR without undue lasting toxicity and to use these as induction therapy followed by treatment with a lower side-effect profile (eg, immunomodulators) to expand on this response. Such induction regimens include cyclophosphamide, doxorubicin, vincristine, and prednisone[295]; MTX, cyclophosphamide, vincristine, and prednisone[296]; and etoposide, idarubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.[297] One must consider the powerful effect of skin-directed therapy, most notably total skin electron beam therapy (TSEBT)[291,293,298-300] but also topical nitrogen mustard,[301-303] in any sort of multimodality regimen.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

The concept of high-dose combination chemotherapy followed by autologous bone-marrow transplantation or peripheral blood stem cell support has curative potential in various non-Hodgkin lymphomas, but experience in CTCL is limited. Autologous hematopoietic stem cell transplantations (HSCT) have yielded disappointing results in patients with MF. Most cases have been reported in patients with advanced stages of MF. Despite reported effective responses with CR in many treated patients (~75%), 18 of 22 (~80%) have relapsed within a mean of 5.8 months (2-14 months).[304-308] The duration of remission in various types of CTCL does not seem to be related to the stage of the disease or absence of a detectable T-cell clone in the harvest.[307]

Allogeneic HSCT are known to achieve much more durable CRs and provide a potentially curative treatment option for advanced MF.[309-311] A proposed graft-versus-lymphoma effect is thought to be responsible for higher effectiveness of allogeneic transplantations. It does, however, carry a higher risk of treatment-related morbidity and mortality such as life-threatening infections and graft-versus-host disease. Reduced-intensity nonmyeloablative allogeneic HSCT may deliver a graft-versus-lymphoma effect with lesser toxicities related to the conditioning regimen. The published experience of allogeneic HSCT in advanced stages of MF/SS have demonstrated some durable long-term remissions.[311-314] A response duration as far as 9 years posttransplantation in a patient with SS/stage IVA disease has been reported.[312] A recent meta-analysis that compared the outcome of allogeneic versus autologous HSCT in patients with advanced MF/SS (97% ≥ stage IIB) using 39 cases from the literature showed a significantly better outcome for patients who received allogeneic HSCT.[315] Five-year overall survival was 80% in the allogeneic transplantation group (n = 20) compared with 23% in the autologous transplantation group (n = 19). The incidence of graft-versus-host disease was high (90%) in patients with myeloablative and nonmyeloablative allogeneic transplantation.

Review of the literature has identified 22 patients with SS whose disease was clearly defined and who received allogeneic HSCT. Most were from small case series or case reports except for the M.D. Anderson Cancer Center experience that included 14 patients designated as SS, of which at least 11 fulfilled the ISCL definition of T_4B_2 staging. Twenty of the 22 patients received a reduced-intensity (nonmyeloablative) regimen (Table IV).[311-314,316-319] Overall outcome results are encouraging. Of the 22 SS allogeneic HSCT recipients reviewed, 15 patients were alive and disease free at a mean posttransplantation follow-up of 44 months (range 18-109 months). The durable remissions were associated with chronic graft-versus-host disease in all but 5 patients. Allogeneic HSCT should be a consideration as a potentially curative option in patients with SS and aggressive and advanced disease resistant to standard treatment. However, once patients develop nodal large cell transformation, overall efficacy may be reduced (A. Rook, MD, unpublished data).

ADJUVANT AGENTS
Topical and systemic steroids

Topical and systemic corticosteroids are mainstays of treatment for patients with SS. Corticosteroids may help SS in several ways including a direct anti-inflammatory effect and induction of apoptosis in malignant lymphocytes.[180] The use of these agents has such a positive effect on quality of life for patients with SS that it is difficult to withdraw them for the purpose of clinical trials or to prevent long-term toxicity. Unfortunately, in patients with SS

who are long-term users, discontinuation of either topical or systemic steroids is also usually associated with a flare of disease. Adverse effects of these agents may include skin atrophy with chronic use of topical steroids and adrenal suppression and/or osteoporosis with either widespread application of topical steroids or the use of systemic steroids.

Phototherapy

PUVA combines the photosensitizing drug psoralen with long-wave (320-400 nm) UV light. Ingested psoralen is activated by UVA that then binds covalently and reversibly to DNA forming bifunctional adducts to pyrimidine bases.[320] The net effect includes inhibition of cellular DNA synthesis, lymphocytotoxicity, and, with long-term use, decrease in circulating helper cells.[321,322] NBUVB (311 nm), which does not require the use of sensitizing agents, has been reported to suppress the function of Langerhans cells and cytokine production from keratinocytes.[323]

Outside of TSEBT, PUVA is the skin-directed therapy most likely to induce a cutaneous CR in all skin stages of MF. Combination therapy in MF/SS of various systemic immunomodulators with PUVA[56,95,116] has shown enhanced efficacy but the one randomized trial in this area failed to show an improvement of etretinate or isotretinoin in conjunction with PUVA (73% OR) over PUVA alone (72% OR) in 69 patients with early MF.[324] NBUVB has been used in combination with immunomodulators as well but no randomized study of monotherapy versus combination therapy or comparison of PUVA versus NBUVB used in combination with systemic therapy in MF/SS has been performed. Lowe et al[325] reported on the use of PUVA with chemotherapy in a patient with SS with 20,000 WBC: on failing prednisone and cyclophosphamide, PUVA was added leading to clearance of the erythroderma and pruritus in only 14 PUVA treatments.

There are several reports of PUVA monotherapy in SS. Kovary et al[326] noted 4 patients with SS (erythroderma plus 60%-80% SCs on buffy coat evaluation): all 4 patients had a good to excellent skin response but no change in the blood involvement or adenopathy. They noted that efficacy depended on increasing the UVA despite the initial discomfort that most patients with SS experience and that continued PUVA was necessary to maintain the response (as opposed to that seen in early MF). Molin and Volden[327] used a short course of systemic steroids to prevent this initial increased photosensitivity. Masui et al[323] has reported on a patient with SS with 23% SCs, CD4/CD8 ratio of 31, adenopathy, and keratoderma who failed PUVA

but who responded to NBUVB and potent topical steroids with both clearing of the skin and blood. Thus phototherapy may affect both the skin and blood tumor compartments in MF/SS. Publications using PUVA or NBUVB in combination with other therapies in the treatment of SS are shown in Table II.

Side effects of both NBUVB and PUVA include potential pain, sunburn, and an increased risk of nonmelanoma skin cancer. Additional side effects with PUVA include nausea with psoralen ingestion, potential for eye damage if inadequate protection from UV light for 24 hours postingestion of psoralen, and an increased risk of melanoma.[328]

Topical mechlorethamine (nitrogen mustard)

Mechlorethamine in an aqueous or ointment-based formulation has been a mainstay in the treatment of MF for more than 50 years. This has been used as primary therapy with curative potential in early disease[329] or after TSEBT to prolong remissions in the skin.[330] It has also been used in conjunction with systemic therapy, including chemotherapy, in more advanced disease. The main immediate side effects of topical mechlorethamine are irritancy and an allergic contact dermatitis but importantly, its use does not cause myelosuppression. There have been several publications about the long-term added risk of nonmelanoma skin cancer in patients treated with topical nitrogen mustard[329] but it has been difficult to sort out the effect of other carcinogenic treatments (phototherapy and/or radiation) also commonly used in the sequential treatment of most patients with MF. No specific study has addressed the adjuvant use of topical mechlorethamine specifically in patients with SS. Topical nitrogen mustard has been used in combination with ECP, interferon alfa, and MTX in 3 patients with SS.[90]

Leukapheresis

There have been a number of older reports of the use of leukapheresis in the treatment of SS.[225,331,332] Most of the reports have combined intermittent leukapheresis with various forms of chemotherapy. Although there are no controlled trials to compare the combination with chemotherapy alone, certain conclusions can be made from the authors' reports. First, leukapheresis was well tolerated. Second, it appeared to make a positive impact on the disease, including pruritus and SC counts, even in those with normal leukocyte count. From the Mayo Clinic experience, McEvoy et al[225] felt that the results with leukapheresis in combination with chlorambucil and prednisone were better than the chemotherapy alone and affected both quality of life and

survival (Table II). Other reports indicate that the response to leukapheresis is short-lived with less improvement over time.[284]

Total skin electron beam radiation

Lymphoma cells generally suffer an apoptotic death when exposed to radiation.[333] They are sensitive to very low doses of radiation given that there is typically no shoulder on the cell survival curve, which in this case is typically linear. There may be other contributing factors in the cutaneous environment that are stimulated by radiation exposure that may contribute to lymphocyte demise.

It is generally acknowledged that TSEBT should be used in conjunction with multimodality therapy if nodal, blood, or visceral involvement is present unless palliation alone is the objective. However, it is extremely useful to determine the extent of improvement that TSEBT alone adds to the treatment regimen before considering the results of multimodality therapy that include TSEBT. Patients with SS have not been evaluated separately in any report of TSEBT but the experience in E-MF/SS sheds valuable light on its potential effects in this type of MF skin disease. The largest studies in E-MF/SS have been those combined from the Yale and the Ontario Cancer Clinic experience. Jones et al[334] evaluated a group of 45 patients with MF/SS and erythroderma, all of whom were treated in a similar fashion and had never received neoadjuvant (pre-TSEBT), concomitant, or adjuvant (post-TSEBT) therapies. Twenty-two patients received less intensive radiation (9 patients <20 Gy and 13 patients 20-30 Gy) and 23 patients received more intensive radiation (32-40 Gy). Blood involvement (>5% SCs) was present in 21 patients. Although the immediate response did not appear to be affected by blood involvement with 100% OR on skin evaluation, the median overall and cause-specific survival (3.4 and 5 years, respectively) were negatively effected by blood involvement based on multivariate analysis. In addition, the dose of radiation affected the amount of histologic clearing in the skin: 74% versus 45% with the more versus less intensive regimen. This confirmed earlier findings that a dose more than 2500 Gy gives enhanced results in patients with erythroderma[335] with more than 3000 Gy giving the best overall response in MF.[336] Introcaso et al[96] have recently shown impressive responses to TSEBT alone in both the skin and blood compartment in patients with SS defined according to present ISCL criteria. Four patients with SS who were all already on systemic immunomodulator therapy for more than 12 weeks (interferon alfa in one patient; interferon alfa plus ECP in two patients; and interferon alfa, bexarotene,

and ECP in a fourth patient) had a CR in the skin and a marked decrease in the circulating lymphocytes including the $CD4^+/CD7^-$ and $CD4^+/CD26^-$ population and CD4/CD8 ratio on treatment with TSEBT. This raises two potential uses of TSEBT in patients with SS: palliative and debulking of not only the skin, but the blood tumor compartment as well.

Several other studies have addressed multimodality therapy using TSEBT. In another series published by Wilson et al,[337] a different group of 44 patients with erythroderma who received TSEBT were retrospectively evaluated. All patients received a higher dose of TSEBT (minimum of 32 Gy) and 21 of these patients also received ECP that was offered neoadjuvantly, concomitantly, or after TSEBT for a median of 6 monthly cycles. A total of 59% of the patients had more than 5% SCs at the time of TSEBT initiation. The CR rate was 73% (not biopsy confirmed) for all 44 patients, 71% for those on monotherapy, and 74% for those with combination therapy. The 3-year disease-free survival for CRs was 49% for those on TSEBT alone and 81% for those receiving a combination of TSEBT and ECP. After adjustment for stage and hematologic involvement, the use of ECP was associated with improvement in cause-specific survival (multivariate P = .048). Hence, the combination of TSEBT and ECP in patients with E-MF/SS appears to potentially enhance clinical outcomes compared with TSEBT alone.

Combination of TSEBT with chemotherapy has been addressed in several studies. Duvic et al[299] treated 44 patients with advanced MF/SS with a 4-month induction regimen of isotretinoin and interferon alfa-2b followed by 6 cycles of alternating the combination of cyclophosphamide, MTX, etoposide, and dexamethasone with the combination of doxorubicin, bleomycin, and vinblastine or with the combination of cyclophosphamide, MTX, etoposide, and dexamethasone alone before TSEBT 28 to 32 Gy in 44 patients with advanced disease. There was an OR rate of more than 60% after induction with immunomodulators alone and 73% after chemotherapy plus TSEBT with 70% of the CRs coming after the TSEBT. Disease-free survival was 7 months. Three studies failed to show any prevention of relapse by 3 different regimens of chemotherapy given post-EB in patients with advanced MF, including 6 monthly cycles of mechlorethamine or cyclophosphamide in conjunction with vincristine, procarbazine, and prednisone (MOPP or COPP)[338]; cyclophosphamide, vincristine, and prednisone[300]; or 6 monthly cycles of doxorubicin and cyclophosphamide.[339,340] Two studies have shown potential efficacy of combined therapy. Griem et al[341] showed

a positive prolongation of the disease-free interval post-TSEBT with the addition of MOPP or COPP. Bunn et al[291] reported on a regimen of relatively low-dose TSEBT (24 Gy) with concomitant and adjuvant multiagent chemotherapy (total 54 weeks) with vinblastin, doxorubicin, bleomycin-cytoxan, MTX, prednisone (VAB-CMP) in patients with stage IIB to IVB MF/SS. On comparison with historical controls at Stanford University Medical Center treated with TSEBT alone (dose of radiation not addressed), there appeared to be increased survival with the combination therapy over TSEBT alone.

The best results with TSEBT are based on a highly fractionated regimen of 32 to 36 Gy with appropriate shielding as per standard protocol. A fractionated regimen over 9 weeks is recommended in an effort to minimize both acute and chronic effects. Given the technically complicated nature of TSEBT, it is recommended that it be provided at centers with experience in the technique.[342]

All patients who receive TSEBT will experience skin erythema, hair loss, and hyperpigmentation. Nail dystrophy and lower extremity edema occur in approximately 50%, and a minority of patients will experience lower extremity edema and bullae when such therapy is administered with a 36-fraction course, 4 days per week. Some patients will experience decreased sweating and difficulty with body temperature control. Late side effects include an increased incidence of nonmelanoma skin cancers. Both acute and chronic radiation dermatitis may occur.

Antipruritic therapy

Although patients with early-stage MF generally have pruritus limited to involved areas, patients with more advanced disease, particularly those with SS, commonly report severe, diffuse, and less well-defined pruritus. Pruritus may become so severe and debilitating that it can result in poor health-related quality of life.[343] Patients with SS may also describe pain, burning, tightness, and sharp pins-and-needles sensations similar to established neuropathic pain syndromes such as diabetic neuropathy, post-herpetic neuralgia, and neuropathic cancer pain.[344] In a recent quality of life survey using the Skindex-29 and EORTC Quality of Life Questionnaire (QLQ)-C30, patients with SS had the worst health-related quality of life compared with patients with MF or cutaneous B-cell lymphoma.[345]

The exact pathophysiology of pruritus in SS is not known. It is likely a result of several contributing factors, including peripheral blood cytokine imbalance, skin infiltration by neoplastic cells, superinfection, and an impaired epidermal barrier with transepidermal water loss. The management of pruritus is therefore challenging. The generous use of moisturizers and nonirritating creams and judicious use of antihistamines is critical to helping relieve this. Patients with SS are known to have a high colonization by *S aureus*[346] and antibiotic treatment has been shown to result in both clinical improvement[346] and diminished pruritus. In some patients, the use of gabapentin, a first-line treatment in the management of neuropathic pain,[347,348] has helped manage pruritus.[349] Titrating the dose of gabapentin upward slowly and using doses of 900 to 3600 mg per day in two or three divided doses can be effective. The primary adverse effect, sedation, may allow patients with SS to sleep and function better in the daytime and the PK of gabapentin make drug interactions unlikely.[344,348] If gabapentin is not effective enough at night, substituting the evening dose with a low dose of mirtazapine 7.5 to 15 mg will help ensure sleep. Mirtazapine has a wide therapeutic index and can be used safely with other medications.[350] A report of the effectiveness of topical naloxone[351] for pruritus in MF supports the opinergic pathways as potentially related to this process and opens the door for evaluation of systemic opioid antagonists in the treatment of pruritus in MF/SS. Most recently, 3 patients with SS were treated with 80 mg a day of aprepitant, an oral neurokinin-1-receptor antagonist widely used as an antiemetic agent in chemotherapy-induced nausea and vomiting, with more than 75% improvement in pruritus.[352] The treatment of the disease itself with targeted therapies will also help manage pruritus.

The effect on pruritus of new therapeutic agents for MF and SS has been addressed and measured in several recent clinical trials. A relevant aspect of this evaluation is the definition of "pruritus relief" used in two recent reports of MF/SS treated with HDAC inhibitors. In the phase IIB study of vorinostat in stage IB to IV MF and SS, pruritus relief was defined as $\geq$ 3-point reduction in those with pruritus score of $\geq$ 3 points at baseline or complete reduction of pruritus, both for $\geq$ 4 continuous weeks without an increase in antipruritic medication. Treatment with vorinostat was associated with pruritus relief in 21 of 65 patients (32%) whose pruritus was 3 or higher at baseline and in 13 of 30 patients (43%) with severe pruritus (a baseline score of 7 to 10 points[41]); antihistamine use was not excluded. In the trial of romidepsin, significant pruritus relief was defined by a decrease of 30 mm or more from baseline on a 100-point VAS (similar to the vorinostat study) or a pruritus score of 0 for two or more consecutive cycles. By this definition and with the exclusion of steroid and antihistamine use, 25 of 52 (48%) patients experienced significant pruritus relief.[353] Of note in an in-depth study of the impact of pruritus on

health-related quality of life of 20 patients with MF and SS, the median change (decrease on a 10-point VAS) in pruritus as reported by patients to represent a meaningful improvement was 3, in line with what both vorinostat and romidepsin trials have used (M-F Demierre, MD and E. Olsen MD, unpublished data). In other trials, it has been reported that the anti-CD52 mAb, alemtuzumab, currently used in SS, improves pruritus in responders.[270]

What is not yet clear is the degree by which improvement in pruritus correlates with OR. In the aforementioned vorinostat trial, significant relief from pruritus was observed in 47.6% of the 21 patients with an OR and in 25.5% of 51 patients without an OR.[41] In the recent romidepsin pivotal trial, clinically meaningful improvement in pruritus was observed in 28 (43%) of 65 patients with moderate to severe pruritus at baseline, which included 11 patients who did not achieve an objective disease response.[255] There is a wide number of agents commonly used in SS, such as bexarotene, interferon, and ECP, in which their impact on pruritus has not been evaluated so that comparative information between treatments is lacking.

RECOMMENDATIONS FOR THERAPY

With few exceptions, there is a dearth of efficacy data on therapeutic agents used to treat patients with SS. This is a result of several factors including that frequently the response for patients with SS is not reported separately from patients with advanced MF and/or the number of patients with SS in any given trial is small either because of the relative paucity of patients with SS compared with MF or because patients with SS are specifically excluded from study inclusion. This review has also highlighted that there has not until recently been a consistent definition of SS used by investigators and clinicians nor attention to the effect on both skin and blood in any given patient with SS, further narrowing the information available on a meaningful response. In this review, we have focused on the literature available where the diagnosis of SS could be confirmed and where the response definition was clearly delineated. In addition, the collective experience of the authors has been taken into consideration in confirming the list of recommended therapies in Table IV.

Based on the extensive current review of published trials of SS, the following suggestions for treatment of SS are made (Table IV). These suggestions mirror for the most part the recently published NCCN guidelines but have been modified based on this literature review, with the acknowledgement that the number of patients reported with each treatment may be small. Many of the systemic therapies that have shown

Table V. Principles of therapy for Sézary syndrome

- Use disease burden and rapidity of progression as determinants of approach to therapy
- Preserve immune response whenever possible
- Use immunomodulatory therapy before chemotherapy unless burden of disease or failure of prior such therapies warrants otherwise
- Always consider combination therapy, particularly systemic immunomodulatory plus skin-directed treatments, which in general has greater efficacy than monotherapy
- Consider potential *Staphylococcus* infection as cause of worsening disease and maintain low threshold for use of systemic antibiotics to prevent life-threatening sepsis
- Preserve quality of life by aggressive treatment of pruritus

efficacy as monotherapy have not been tested in clinical trials with adjuvant skin-directed therapy or as part of a multimodality therapeutic regimen but of those that have, there has generally been an increase in RR.

There are several important principles that should be considered when selecting therapy for a patient with SS (Table V). Initially, choice of therapy should be based on the relative burden of disease, impact on quality of life, and rapidity with which the disease is progressing. With regard to burden of disease, issues to note include the degree of infiltration of the skin, the presence or absence of tumors on the skin, the extent of lymphadenopathy, the relative burden of circulating malignant T cells, and the rate of increase of the serum lactate dehydrogenase and of the peripheral WBC count. Furthermore, when considering the initial therapeutic approach, whenever possible, preservation of the immune response is exceedingly important. Because the malignant T cells produce soluble factors that are responsible for endogenous immune suppression leading to heightened susceptibility to infection, further suppression of the immune response can have deleterious effects. Therefore, the use of immune modulatory therapies that can augment host immunity, such as interferon alfa or interferon gamma, together with retinoids and/or ECP should be considered as initial treatment choices. The addition of skin-directed therapies can lead to further debulking of tumor cells without producing a significant adverse impact on the immune response.

Thus, combination or multimodality approaches should be encouraged when possible as emerging evidence suggests that higher RRs may be achievable and that responses may occur in a more accelerated manner. For example, use of PUVA with interferon

may enhance RRs in comparison with PUVA alone. Moreover, responses to ECP together with interferon and bexarotene may yield higher RRs when compared with ECP alone. The addition of TSEBT to the latter multimodality regimen will likely further augment responses in the skin and in the peripheral blood compartment. Another combination that deserves further exploration is dual therapy with MTX and interferon alfa, which as summarized previously in this review, may lead to high RRs.

All of the above choices would be suitable for a patient with a new diagnosis and without signs of rapid progression of disease. However, should the patient's progression appear to be rapid, then consideration should be given to the use of a therapeutic approach that might lead to the accelerated removal of large numbers of tumor cells. This might include a chemotherapeutic drug or regimen in category B of Table IV, keeping in mind that many of the chemotherapeutic approaches in category B tend not to be associated with sustained clinical responses or are able to be continued long term for maintenance therapy and are likely to depress the host immune response. Thus, a resumption of immune modulatory therapy should be considered at the earliest possible time. It is noteworthy that immune modulators may be less effective when used immediately after an intensive regimen of chemotherapeutics.

When this approach fails to produce the desired clinical benefit, other agents may be considered that are efficacious and produce short-term immune suppression. An excellent choice for patients refractory to immunomodulators is the mAb alemtuzumab used in a low-dose regimen popularized by Bernengo et al.[42] It is extremely effective at debulking the blood and erythrodermic skin of malignant T cells. Clinical responses can be quite prolonged, and, with the addition of prophylaxis against infection with trimethoprim-sulfamethoxazole, voriconazole, and acyclovir, serious infection rates can be low. The fusion protein denileukin diftitox, which is among agents listed in category A of Table IV, does not appear to profoundly suppress the immune response. However, it is best used among patients with a low circulating burden of malignant T cells as a high tumor burden may serve as a "sink" for this drug leading to an inadequate systemic response at the recommended doses. Refractory patients should also be considered for clinical trials or allogeneic transplantation before the introduction of prolonged courses of multidrug chemotherapy.

We recommend continued evaluation in clinical trials of a combination of skin-directed and single or multiple systemic therapies for SS. It is also obvious from studies where the results in skin and blood have

been reported separately that both may not respond in tandem. Therefore, in future clinical trials of SS, the inclusion of an evaluation of blood tumor burden determined either by flow cytometry or by peripheral blood SCs quantified by a central laboratory and the report of results for SS separately from other patients with MF would help to determine the usefulness of various agents in this subtype of CTCL.

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