TREATMENT OF EARLY STAGE MYCOSIS FUNGOIDES

FOCUS ON SKIN-DIRECTED THERAPY

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THANK YOU CUTANEOUS LYMPHOMA FOUNDATION

- Cutaneous lymphomas comprise a rare group of diseases: annual incidence 0.5-1 new case per 100,000 people.
- May take a long time to establish diagnosis.
- Excellent progress is being made.
- Excellent information is available for clinicians and patients:
 - Clfoundation.org, NCCN.org, Clinicaltrials.gov and others
- There are ongoing efforts to improve classification and treatment.

Table 2Cutaneous lymphomas in the 2016 update of the WHO classification. 12.

Specific entities of mature B-cell neoplasms
Primary cutaneous follicle centre lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Specific or provisional entities of mature T- and NK-cell neoplasms
Hydroa vacciniforme-like lymphoproliferative disease
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides

Mycosis fungoides variants
Pilotropic mycosis fungoides
Granulomatous slack skin
Localized pagetoid reticulosis

Sézary syndrome

Primary cutaneous CD30+ T-cell lymphoproliferative disorders

Lymphomatoid papulosis

Primary cutaneous anaplastic large cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma

Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)

Primary cutaneous acral CD8+ T-cell lymphoma (provisional)

Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder (provisional)

Epstein-Barr virus (EBV) positive mucocutaneous ulcer (provisional)

Other lymphomas with frequent primary cutaneous involvement (a)

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Intravascular large B-cell lymphoma

Adult T-cell leukaemia/lymphoma

Extranodal NK/T cell lymphoma, nasal type

⁽a): a primary cutaneous involvement may occasionally be observed in many other hematological neoplasms, particularly in myelogeneous leukemia ("aleukemic leukemia cutis") and blastic plasmacytoid dendritic cell neoplasm.

Box 1

Classification of cutaneous T-cell lymphomas (World Health Organization 2018)

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD30-positive lymphoproliferative disorders

Lymphomatoid papulosis

Primary cutaneous anaplastic large cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma

Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma

Primary cutaneous acral CD8-positive T-cell lymphoma

Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder

CUTANEOUS T-CELL LYMPHOMAS

Mycosis Fungoides 60%

Sezary Syndrome15%

CD30+ Lymphoproliferative Disorders 20%

Lymphomatoid Papulosis (LyP)

Anaplastic Large Cell Lymphoma (ALCL)

Other rare types

BRIEF HISTORY OF MYCOSIS FUNGOIDES

- 1806: Dr. Jean-Louis-Marc Alibert, a French dermatologist described mushroom-like lesions on the skin of a patient and used the term mycosis fungoides to describe the condition, loosely meaning mushroom-like fungal disease.
- 1870: Dr. Ernest Bazin, (Dr. Alibert's student), described the progression from patches to plaques to tumors in mycosis fungoides

MYCOSIS FUNGOIDES IN HISTORICAL PERSPECTIVE: A UNIFYING CONCEPT

Jul – Sep 2001 I Vol. 7, No. 3 Derm 101

Ackerman, A. Bernard; Paichitrojjana, Anon

MYCOSIS FUNGOIDES

Past, present and future of cutaneous lymphomas

Lorenzo Cerroni

Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria

Seminars in Diagnostic Pathology 34 (2017) 3–14

1806: mycosis fungoides described by Alibert (26 years before Hodgkin's Disease described)

1870: Bazin described patches And plaques preceding nodules

1902: Brocq described "parapsoriasis" As a group of related disorders

1949: Sezary syndrome described.

1974 description of immunologic features of lymphoma



1975: Term "CTCL" introduced

1994: first attempt to classify cutaneous lymphomas based on clinical, biopsy findings, and genetic features

Fig. 1. Lucas, the 56-year-old man who was the patient affected by mycosis fungoides described by Alibert in 1806.¹.

CLINICAL PHASES OF CTCL







Table 1. Clinical Staging System for Mycosis Fungoides and Sézary Syndrome

	TNM Classification				
	Ţ	N	M		
Stage					
IA	T1, limited patch or plaque; <10% BSA	NO, nodes uninvolved	M0, no visceral involvement		
IB	T2, generalized patch or plaque; ≥10% BSA	NO	MO		
IIA	T1-2	N1, nodes enlarged, histologically uninvolved	MO		
IIB	T3, tumors	NO-1	MO		
IIIA	T4, erythroderma	NO	MO		
IIIB	T4	N1	MO		
IVA	T1-4	N3, nodes enlarged, histologically involved	MO		
IVB	T1-4	NO-3	M1, visceral involvement		
B Classification*		= Low risk group			
B0	No circulating Sézary cells				
B1	PBSC >20%, <1000/mm ³ by morphologic traits	= Intermediate risk	group		
B2	Sézary syndrome defined as ≥ 1 of the following: PBSC $\geq 1000/\text{mm}^3$, CD4/CD8 ratio ≥ 10 , CD4+CD7- cells $\geq 40\%$ or CD4+CD26 - cells $\geq 30\%$ of lymphocytes	= High risk group			

MYCOSIS FUNGOIDES AND SEZARY: STAGING

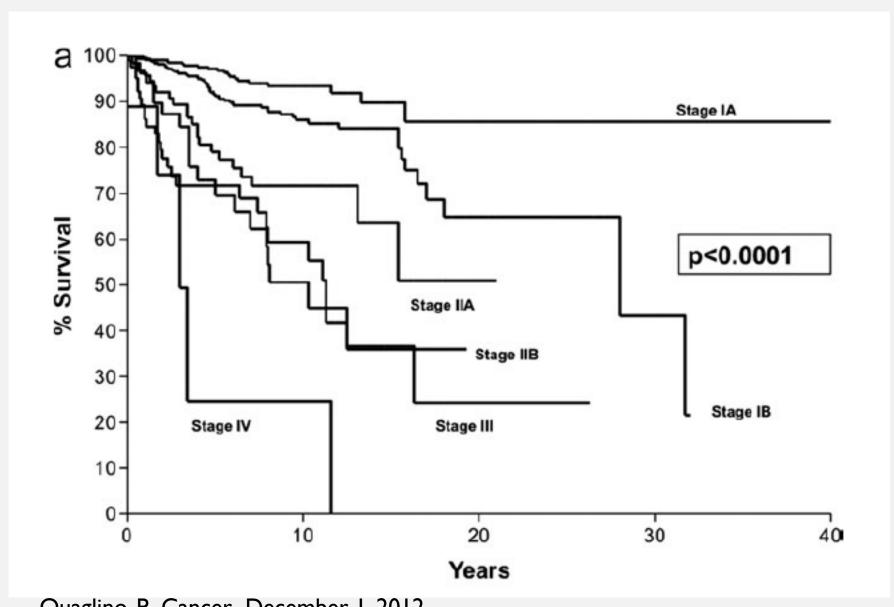
- Stage IA: Patch/ Plaque <10% Body Surface Area
- Stage IB: Patch/ Plaque >10% BSA
- Stage IIA: Patch/Plaque any amount BSA; Lymph node enlargement, (-) histology
- Stage IIB: Cutaneous Tumors
- Stage III: Erythroderma
- Stage IVA and IVB: Malignant infiltration of lymph nodes and viscera

Risk of Progression in Mycosis Fungoides

Maximum stage	IA	IB	IIA	IIB	IIIA	IIIB	IVA1	IVA2	IVB	Disease
Stage at diagnosis										Stage Progression
IA (n=552)	412 (74.6%)	40 (7.2%)	20 (3.6%)	37 (6.7%)	16 (2.9%)	1 (0.2%)	12 (2.2%)	5 (0.9%)	9 (1.6%)	140 (25.4%)
IB (n=556)		396 (71.2%)	24 (4.3%)	63 (11.3%)	29 (5.2%)	7 (1.3%)	14 (2.5%)	12 (2.2%)	11 (2.0%)	160 (28.8%)
IIA (n=122)			73 (59.8%)	12 (9.8%)	12 (9.8%)	2 (1.6%)	9 (7.4%)	11 (9.0%)	3 (2.5%)	49 (40.2%)
IIB (n=78)				44 (56.4%)	6 (7.7%)	0	10 (12.8%)	10 (12.8%)	8 (10.2%)	34 (43.6%)
IIA (n=82)					50 (61.0%)	7 (8.5%)	15 (18.3%)	7 (8.5%)	3 (3.7%)	32 (39.0%)
IIB (n=11)					,	5 (45.5%)	4 (36.4%)	2 (18.2%)	0	6 (54.5%)
IVA1 (n=1)							1	0	0	_
IVA2 (n=9)								8 (88.9%)	1 (11.1%)	1
IVB (n=1)								,	1	_

^aThe number reported is the number of patients (percentages set in parentheses were calculated based on the total number of patients for each stage of disease). Gray-shaded cells represent patients who maintained the stage of disease noted at the time of the initial diagnosis to the end of the follow-up period.

Excellent Overall Survival in Early Stage Disease



Quaglino, P. Cancer December 1, 2012

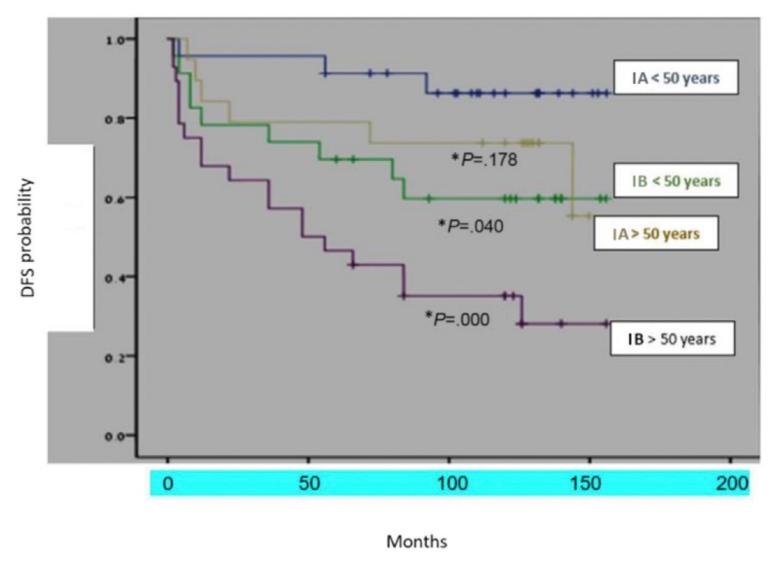


Fig 3. Disease-free survival multivariate analysis by stage and age. *P value relative to stage IA, <50-year group. *DFS*, Disease-free survival.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Primary Cutaneous Lymphomas

Version 2.2019 — December 17, 2018

NCCN.org

Continue

DIAGNOSIS^a

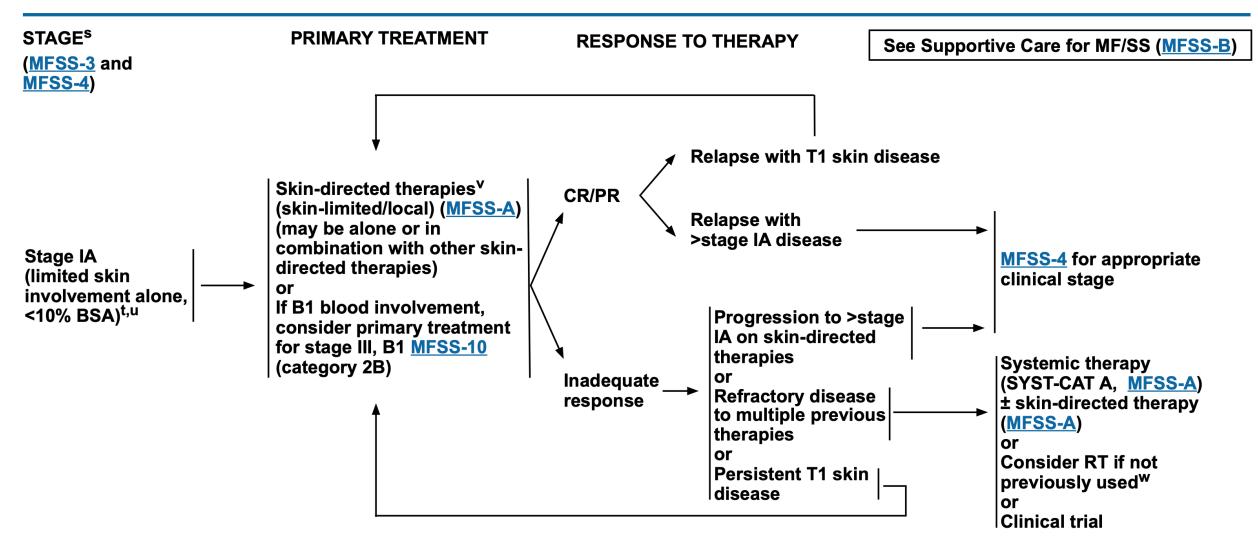
ESSENTIAL:

- Biopsy of suspicious skin sites
- ▶ Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis
- Dermatopathology review of slides^b
- IHC panel of skin biopsy^{c,d,e}
- ▶ CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30
- Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements or other assessment
 of clonality (karyotype, array-CGH, or FISH analysis to detect somatic mutations or genetic alterations)^{a,f}

TNMB		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome ^{I,m}
Skin	T1	Limited patches, ⁿ papules, and/or plaques ^o covering <10% of the skin surface
	T2	Patches, ⁿ papules, and/or plaques ⁿ covering ≥10% of the skin surface
	T2a	Patch only
	T2b	Plaque ± patch
	Т3	One or more tumors ^p (≥1 cm in diameter)
	T4	Confluence of erythema ≥80% body surface area

NCCN Guidelines Version 2.2019 Mycosis Fungoides/Sezary Syndrome

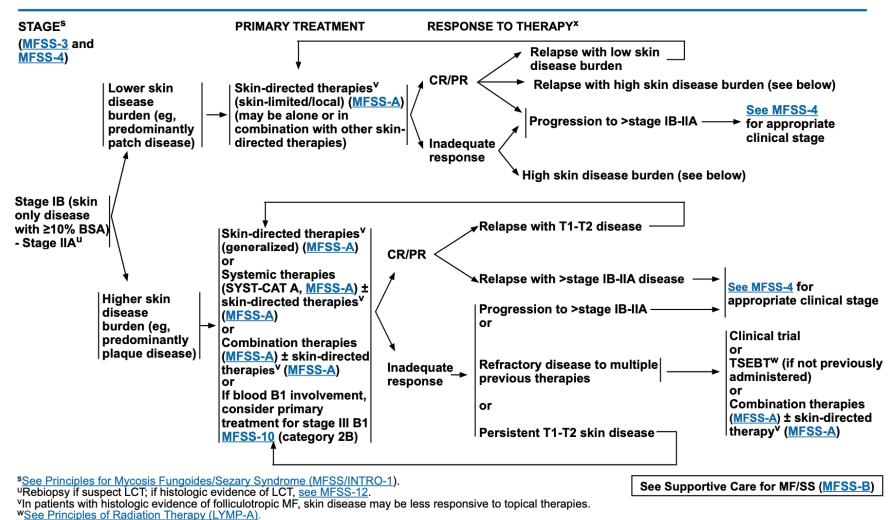
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Cancer Mycosis Fungoides/Sezary Syndrome

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xImaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup.

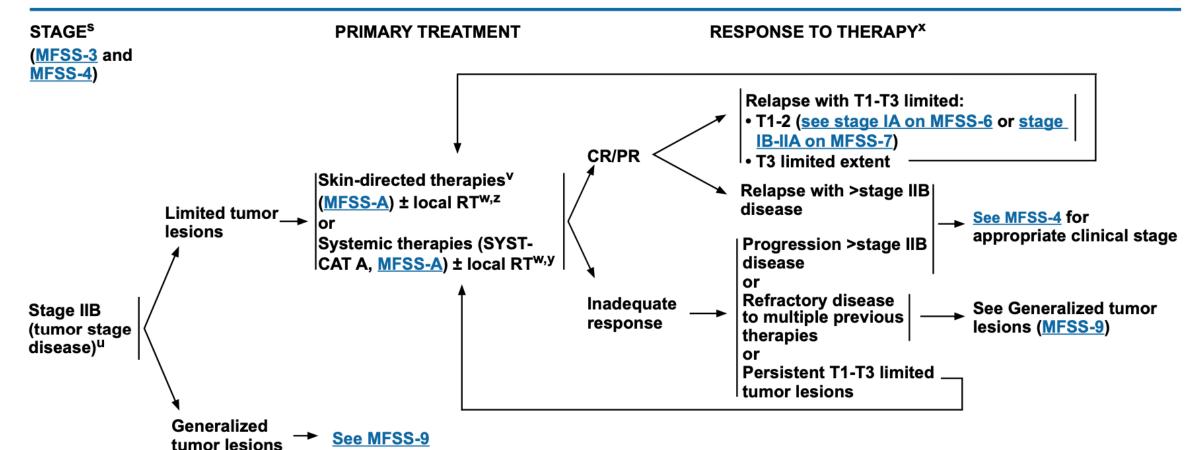
Note: All recommendations are category 2A unless otherwise indicated.

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



NCCN Guidelines Version 2.2019 Mycosis Fungoides/Sezary Syndrome

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NCCN Guidelines Version 2.2019 Mycosis Fungoides/Sezary Syndrome

SUGGESTED TREATMENT REGIMENS^a

SKIN-DIRECTED THERA	APIES APIES
Skin-Limited/Local (For limited/localized skin involvement)	 Topical corticosteroids^b Topical mechlorethamine [nitrogen mustard] Local radiation (ISRT) (8–12 Gy; 24–30 Gy for unilesional presentation)^c Topical retinoids (bexarotene, tazarotene) Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA/UVA-1)^d Topical imiquimod Topical carmustine (category 2B)
Skin-Generalized (For generalized skin involvement)	 Topical corticosteroids^b Topical mechlorethamine [nitrogen mustard] Phototherapy (UVB, NB-UVB, for patch/thin plaques; PUVA/UVA-1)^d TSEBT (12–36 Gy)^{c,e,f}

COMBINATION THERAPIE	S (alphabetical order)
Skin-directed + Systemic	 Phototherapy + ECP^k Phototherapy + IFN Phototherapy + retinoid TSEBT + ECP^h
Systemic + Systemic	 ECP^k+ IFN ECP^k + retinoid ECP^k + retinoid + IFN Retinoid + IFN

GOALS OF SKIN DIRECTED TREATMENT

- Used mainly for Stage IA-IIA, but also used in combination with systemic treatment
- Quality of life: minimize itching, discomfort, dry skin, sense of well-being.
- Aim for remission... but recognize that complete cure is not likely*
- Provide a treatment that is effective, and manageable.

Pruritus

- Assessment
- > Pruritus should be assessed
- ▶ Correlation between sites of disease and localization of pruritus may be useful in tailoring therapy
- ▶ For severe or persistent pruritus despite therapeutic response other potential causes for pruritus should be investigated
- Treatment
- ► Co-management with a dermatologist with expertise in skin care and CTCL
- ▶ Optimized skin-directed and systemic therapy for MF/SS
- ▶ Mild, unscented soaps for bathing are gentle and optimal to prevent skin dryness
- **▶ Moisturizers/ emollients**
- ▶ Topical steroid application (appropriate strength for body region) ± occlusion¹
- **▶** Topical over-the-counter preparations
- **▶** Systemic agents
 - **♦** First-line
 - H1 antihistamines; single agent or combination of antihistamines from different classes²
 - Gabapentin^{3,4}
 - **♦ Second-line**
 - Aprepitant⁵⁻⁸
 - Mirtazapine⁴
 - Selective serotonin reuptake inhibitors⁹
 - **♦ Third-line**
 - Naltrexone¹⁰

TOPICAL CORTICOSTEROIDS

- First-line treatment for patch stage
- Immunomodulatory and anti-inflammatory effects
 - Down regulation of cytokine production
 - Promotion of inflammatory mediators
- Ease of use. Applied to individual lesions
- "Pulse" alternating class I with class III or IV
- Multiple vehicles allow help for dry skin and itch
- Local Side Effects with prolonged use
 Before and After 2 week application potent topical steroid







TEMOVATE* Ointment, 0.05% (clobetasol propionate) TEMOVATE Ointment is more potent than Diprolene * and Psorcon* Ointments; comparative studies of TEMOVATE * Cream, 0.95% and Diprolene * Cream are pending.*	High Potency	Diprolene * Ointment, 0.05% Psorcon * Ointment, 0.05% TEMOVATE * Cream, 0.05% (clobetaso) propionate) Diprolene * Cream, 0.05%
Cyclocort* Ointment, 0.1% Diprosone* Ointment, 0.05% Florone* Ointment, 0.05% Halog* Cream, 0.1% Lidex* Cream, 0.05% Lidex* Gel, 0.05%	II	Lidex® Ointment, 0.05% Maxiflor® Ointment, 0.05% Topicort® Cream, 0.25% Topicort® Gel, 0.05% Topicort® Ointment, 0.25%
Aristocort A* Ointment, 0.1% Diprosone * Cream, 0.05% Florone * Cream, 0.05%	III	Maxiflor® Cream, 0.05% Valisone® Ointment, 0.1%
Cordran® Ointment, 0.05% Kenalog® Cream, 0.1% Synalar® Ointment, 0.025%	IV	Topicort® LP Cream, 0.05% Westcort® Ointment, 0.2%
Cordran ® Cream, 0.05% Diprosone ® Lotion, 0.02% Kenalog ® Lotion, 0.1% Locoid ® Cream, 0.1%	٧	Synalar® Cream, 0.025% Valisone® Cream, 0.1% Westcort® Cream, 0.2%
ACLOVATE * Cream, 0.05%² (alclometasone dipropionate) ACLOVATE * Ointment, 0.05%² (alclometasone dipropionate) DesOwen * Cream, 0.05%	VI	Locorten® Cream, 0.03% Synalar® Solution, 0.01% Tridesilon® Cream, 0.05% Valisone® Lotion, 0.05%
Topicals with hydrocortisone, dexamethasone, flumethalone,	VII Low Potency	prednisolone, and methylprednisolone

NITROGEN MUSTARD

- Used for chemical warfare during WWI (Mustard Gas)
- Goodman and Gilman discovered effectiveness in treating lymphomas in mice 1942, but publication was postponed until 1946.
- First drug approved for systemic treatment of lymphoma

Topical Nitrogen Mustard Approved

August 26, 2013

Ceptaris Receives FDA Approval for VALCHLOR™ (mechlorethamine) Gel for the Treatment of Stage IA and IB Mycosis Fungoides-Type Cutaneous T-Cell Lymphoma in Patients Who Have Received Prior Skin-Directed Therapy

First and only FDA-approved topical formulation of mechlorethamine (nitrogen mustard)

Patient support and assistance programs to be established for VALCHLOR

NITROGEN MUSTARD TIME TO RESPONSE

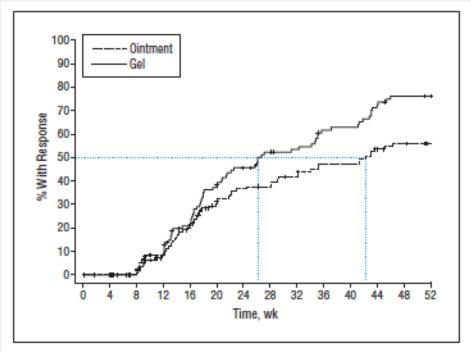


Figure 3. Kaplan-Meier curves for time to response by Composite Assessment of Index Lesion Severity in the intent-to-treat population, showing that estimated times to a 50% response are 26 weeks in the gel arm and 42 weeks in the ointment arm.

Lessen, S: JAMA Dermatology January 2013

NITROGEN MUSTARD SIDE EFFECTS

	Received Allocated Intervention, No. (%)			
Event	Gel (n = 128)	Ointment (n = 127)	Total (n = 255)	
Skin irritation ^a	32 (25.0)	18 (14.2)	50 (19.6)	
Pruritus	25 (19.5)	20 (15.7)	45 (17.6)	
Erythema	22 (17.2)	18 (14.2)	40 (15.7)	
Contact dermatitis	19 (14.8)	19 (15.0)	38 (14.9)	
Skin hyperpigmentation	7 (5.5)	9 (7.1)	16 (6.3)	
Folliculitis	7 (5.5)	5 (3.9)	12 (4.7)	

 $^{^{}a}P$ = .04, Fisher exact test.

INTRICACIES OF NM THERAPY







- Cost issues
- NM considered carcinogen *caution with household exposures & disposal of product
- Irritant reactions and true allergic reactions
- Less-frequent toxicities
 - Myelosuppression/ nonmelanoma skin cancers

Photographs courtesy of T.S. Kupper MD

THERE ARE SOME IMPORTANT THINGS TO KNOW BEFORE STARTING TARGRETIN GEL TREATMENT:

- TARGRETIN gel can cause major damage to a fetus.

 If you are capable of becoming pregnant, you should take
 contraceptive measures to avoid pregnancy before, during,
 and after treatment. It is recommended that 2 reliable forms of
 contraception be used together.
- DO NOT use insect repellents containing DEET (N,N-diethylm-toluamide) or other products containing DEET while using TARGRETIN gel.
- DO NOT take more than the recommended daily dietary allowance of vitamin A (4000 to 5000 International Units).
- Minimize exposure to sunlight and artificial ultraviolet light (sunlamps, tanning beds, etc.).

GEL VEHICLE

- Local site reactions
 - Erythema
 - Itch
 - Burning

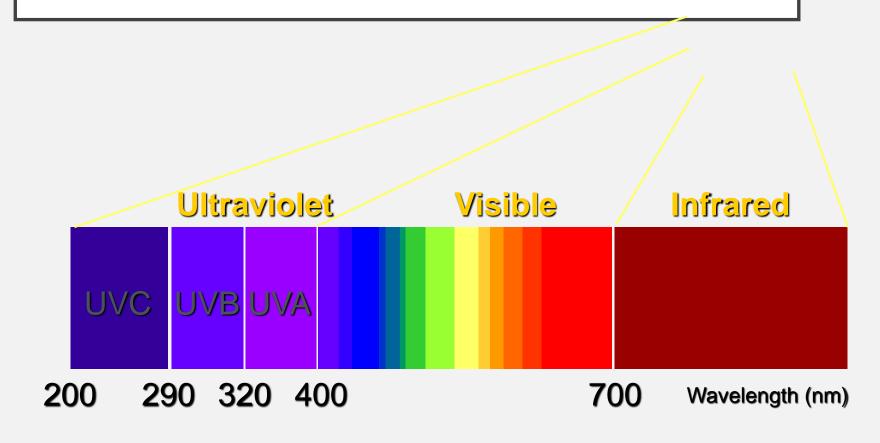
Start out gradually



PHOTOTHERAPY

- UV light therapy is one of the most widely used—skin directed therapies for early stage CTCL
- Benefits of UVL anecdotally described with outdoor sun exposures
- Selected when skin involvement more diffuse/topical impractical
 - Broad band UVB (290-320nm)
 - Narrow band UVB (311nm)
 - PUVA—psoralen + UVA (320-400nm)

THE UV SPECTRUM COMPRISES 3 RANGES

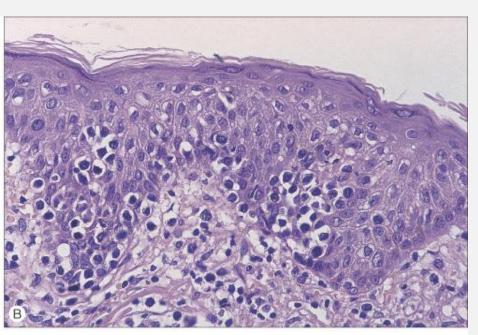


MECHANISM OF ACTION

- Immune mechanism of ultraviolet light is broad
- Effects produced on surface membrane proteins & soluble mediators
- Induces apoptosis (cell death)
- Ultraviolet B is active in epidermal keratinocytes and Langerhans' cells
- Ultraviolet A penetrates deeper into dermis reaching dermal fibroblasts, infiltrating inflammatory cells and dendritic cells

IB PATCH/PLAQUE PHOTOTHERAPY CANDIDATE





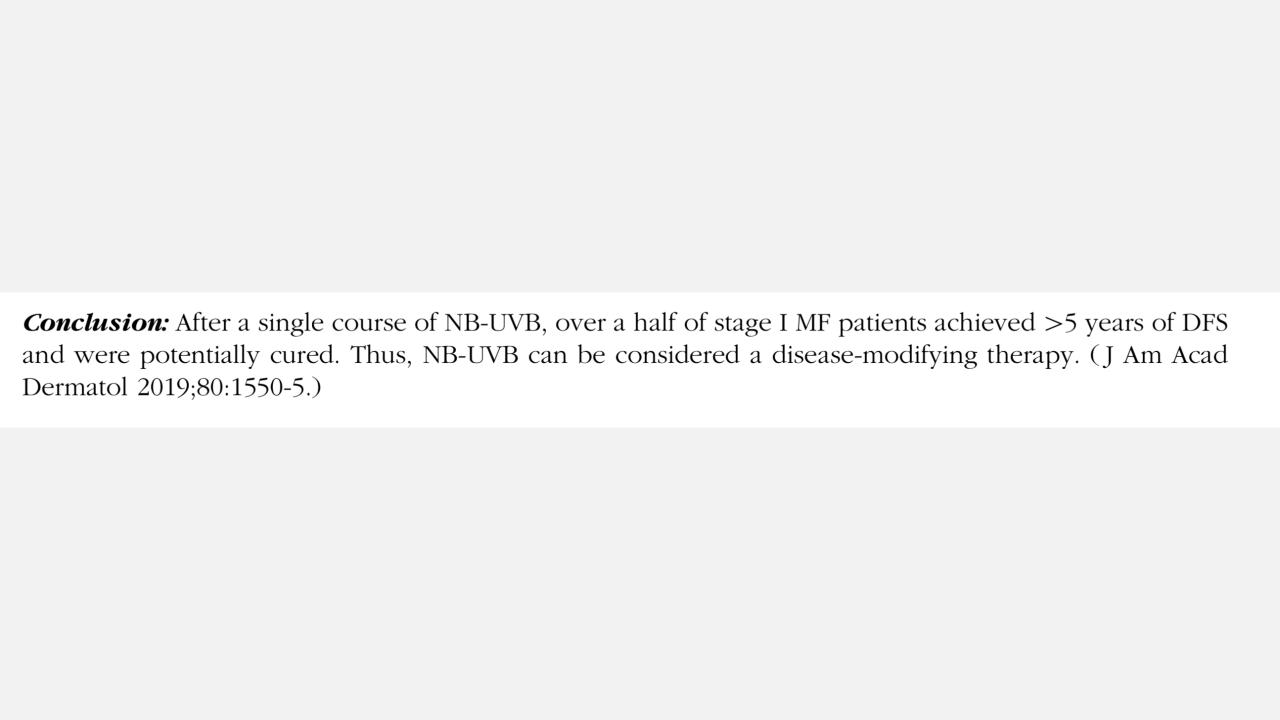
© 2003 Elsevier - Bolognia, Jorizzo and Rapini: Dermatology - www.dermtext.com

LOGISTICS OF PHOTOTHERAPY

- Usually carried out in dermatology offices. Home ultraviolet boxes may be obtained with supervision if insurance company agrees.
- Tanning booth not usually advised.
- 2-3 times per week until remission.
- Goal is clinical response with eventual taper to maintenance schedule.
- Time consuming. Geographically challenging.

Potential of narrow-band ultraviolet B to induce sustained durable complete remission off-therapy in patients with stage I mycosis fungoides

Felix Pavlotsky, MD, a,b Marwan Dawood, BA,b and Aviv Barzilai, MD e,b Tel Hashomer and Tel Aviv, Israel



Results: Of the 117 patients who started NB-UVB, 93 patients (80%) had a complete response and 56 (60%) were disease free as of March 2017. In a multivariate analysis, DFS was affected independently by age and disease stage only. DFS was longer for patients <50 years old (124 months) than those \geq 50 years old (91 months, P = .01) and longer for stage IA patients (131 months) than stage IB patients (87.6 months, P = .001).

CAPSULE SUMMARY

- Narrow-band ultraviolet B (NB-UVB)
 produces high rates of complete
 response for patients with stage I
 mycosis fungoides. Data on long-term
 remission off therapy are lacking.
- NB-UVB induced >5 years disease- and therapy-free survival in \sim 60% of complete response patients.
- NB-UVB can be considered a diseasemodifying and potentially curative therapy for patients with stage I mycosis fungoides.

RADIATION THERAPY

- Total body for widespread disease
- Wide field dose over period of 9-10 weeks
- Penetrates 5 mm into skin, total dose 36 Gy
- Local radiation for limited tumors/thick plaques

TOTAL SKIN ELECTRON BEAM THERAPY (TSEBT)

- TSEBT delivers treatment to wide field (skin) while ensuring patient safety
- Technically challenging
- Specialized Centers





SIDE EFFECTS

Redness (burns possible)

Dryness and Itching

Hair and nail loss

Inability to **sweat**

Eye irritation

Lower extremity swelling

Temperature dysregulation





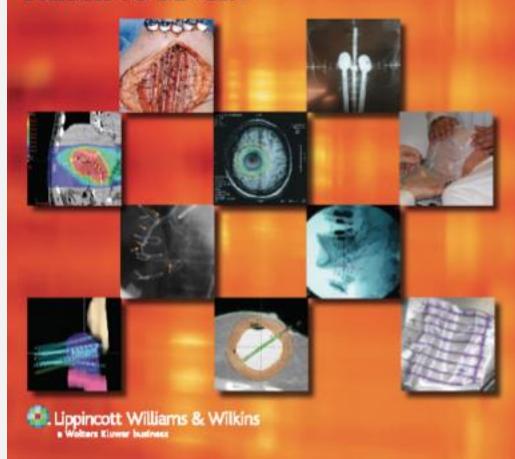
Moisturizers for dryness, sunscreens for protection from UV exposure, artificial tears for dry eyes

- Lifetime limitation
- Rigorous regimen, specialized centers, expensive

BRACHYTHERAPY

Applications and Techniques

PHILLIP M. DEVLIN



FEET, SET-UP



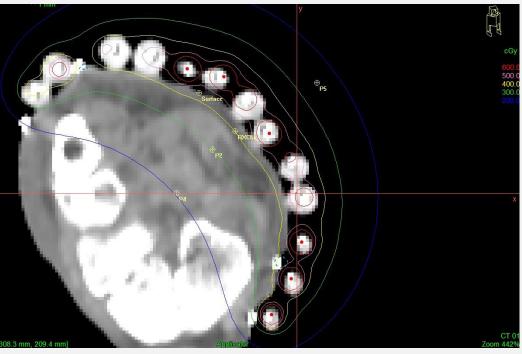






FEET, ISODOSE











Local radiation and phototherapy are the most cost-effective treatments for stage IA mycosis fungoides: A comparative decision analysis model in the United States

Fan Di Xia, MD,^a Bart S. Ferket, MD, PhD,^b Victor Huang, MD,^c Robert S. Stern, MD,^d and Peggy A. Wu, MD, MPH^d

Boston, Massachusetts, and New York, New York

Journal of the American Academy of Dermatology 2019; Feb: 80 (2) 485-492

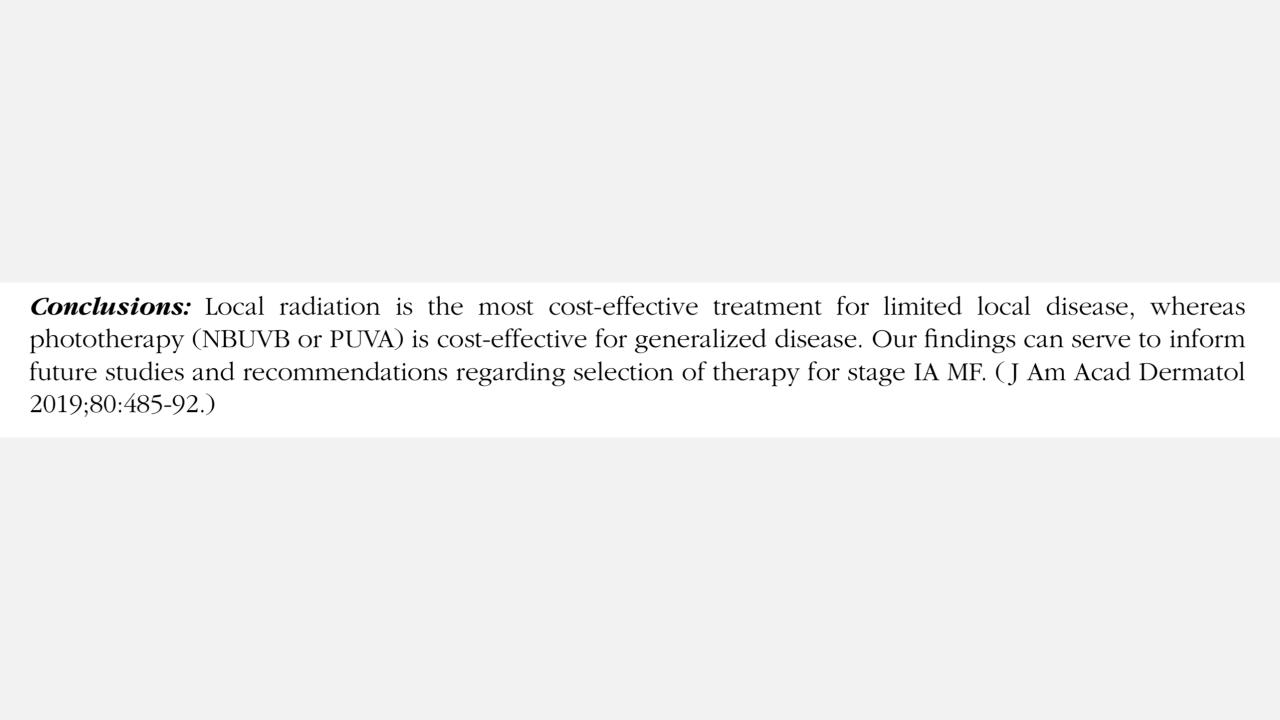


Table II. Cost for 3-month cycle by treatment option

Treatment option	Baseline cost
Topical corticosteroids	\$1214
Topical nitrogen mustard	\$17,469
Topical bexarotene	\$384,059
PUVA	\$10,582
NBUVB	\$5604
Local radiation	\$3484

NBUVB, Narrowband ultraviolet B; PUVA, psoralen plus ultraviolet A.

VITTICIE III I I COO

Stage la mycosis fungoides should be treated until proven otherwise

Pavlotsky Felix, M.D.^{1,3,*}, M.D.^{1,3,*}, Hodak Emmilia, M.D.^{2,3}, Dawood Marwan, M.D.³, Barzilai Aviv, M.D.^{1,3}

DOI: https://doi.org/10.1016/j.jaad.2019.09.001

Journal Pre-proof

Article type: Letter to the editor

Title: Stage la mycosis fungoides should be treated until proven otherwise

Pavlotsky Felix^{1,3} M.D., Hodak Emmilia^{2,3} M.D., Dawood Marwan³ M.D., Barzilai Aviv M.D.^{1,3}

SUMMARY

- The overall prognosis for early stage mycosis fungoides is excellent.
- There are several options for skin directed treatment that may be used singly or in combination.
- Treatment choices will be individualized.
- Let your providers know of quality of life concerns!!

THANK YOU!!

