Treatment of early stage CTCL
Joan Guitart, MD
Chicago, IL USA

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Early CTCL: treatment considerations

- Importance of long term f/u by our CTCL team
- Discussion on expectations: “no cure” aim for a prolonged remission or stable disease.
- Stage and “metastasis” and disease confinement.
- Momentum of disease

92 y. o. man with stable MF T1 for many years

CTCL pts. are at increased risk of other cancers:
Make sure patient is up to date with cancer screening


- NHL ( B cell lymphomas) in men and lung in women
- Urinary tract, HL and NHL in CD30PD

Mycosis fungoides associated with melanoma and dysplastic nevus syndrome
J. A. Pickar, M.D., I. Browett, M.D., and M. Davis, M.D.

Prevalence 2.4%
6/250 pts. RR=15
1. CTCL patients are prone to skin infections
2. Disease burden & pruritus worsens with infections (SA)
3. CTCL patients often die of infections

We must watch for infections

Survival of CTCL directly related to tumor burden

10 year DSS for patch MF patients: T1 100% & T2 88%

2/3 present with early disease

Patch (T2a) better than plaque (T2b) disease

P = .002 DSS

Folliculotropic MF: increased risk of disease progression
(p = 0.005)

Y Kim et al. Arch Derm 2003

Agar et al. JCO 2010
Idiopathic follicular mucinosis versus FMF?

**Indolent FMF**
- Younger
- Less pruritus
- Less destructive or more mucinous, no LCT
- Less bacterial infections

**Aggressive FMF**
- Older
- More pruritus
- Tumors, destructive
- Dense LCT
- Staph infection
Why do we need to treat early mycosis fungoides?

EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome

<table>
<thead>
<tr>
<th>First-line</th>
<th>Recommendation level of evidence</th>
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<tr>
<td>Topical corticosteroids</td>
<td>C 4</td>
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<tr>
<td>PUVA</td>
<td>C 4</td>
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<tr>
<td>UWB (patches only)</td>
<td>C 4</td>
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<tr>
<td>Topical corticosteroids</td>
<td>C 4</td>
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<tr>
<td>Localised radiotherapy</td>
<td>C 4</td>
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<td>TSEB (C3 treatments)</td>
<td>C 4</td>
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<tr>
<td>RIC</td>
<td>C 4</td>
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<td>BMT</td>
<td>C 4</td>
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Poor Evidence for most SDT
Prolonged CR “cure” can be achieved in early CTCL

Topical Nitrogen mustard ~20%

Phototherapy ~ 20-40%

Multilineage progression of genetically unstable tumor subclones in cutaneous T-cell lymphoma

CTCL guidelines: T1 (<10% BSA)

For limited/localized skin involvement (Skin-Limited/Limited)
- Topical corticosteroids
- Topical chemotherapy (mechloretamine [nitrogen mustard], carmustine)
- Local radiation (8-36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, nbUVB for patchy plaques; PUVA for thicker plaques)
- Topical imiquimod
Skin directed therapies more effective than systemic therapies for patch/plaque MF

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CR (%)</th>
<th>ORR (%)</th>
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<tbody>
<tr>
<td>Topical steroids</td>
<td>45-65%</td>
<td>75-95%</td>
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<tr>
<td>Bexarotene gel</td>
<td>20-35%</td>
<td>50-75%</td>
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<tr>
<td>Topical NM</td>
<td>25-70%</td>
<td>50-90%</td>
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<tr>
<td>nsUVB</td>
<td>45-75%</td>
<td>75-100%</td>
</tr>
<tr>
<td>PUVA</td>
<td>50-80%</td>
<td>85-100%</td>
</tr>
<tr>
<td>TSEBT (≥30 Gy)</td>
<td>90-90%</td>
<td>100%</td>
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</table>

T1: Response 94%  
CR 63%  
PR 31%  

- Patch > plaques  
- Not tumors  
- Vigorous application  
- Slow taper

Topical Corticosteroids for Mycosis Fungoides  
Experience in 79 Patients  
Kevin E. Zachariah, MD; Mohammad Karbassi Saberi, MD; Stacie Israel, MD

**Objective:** To determine the effectiveness of topical corticosteroids in the management of cutaneous T-cell lymphoma.

**Design:** Prospective study.

**Setting:** Academic referral centers. Veterans Affairs Medical Center, and private practice.

**Patients:** Twenty-nine patients with plaque or patch stage of cutaneous T-cell lymphoma were treated (mean age 65 years; 17 female, 12 male; 21 with stage I, 6 with stage IIa, and 2 with stage III). The mean duration of disease was 7.5 years, and 73% of patients had received prior systemic therapy. The mean cumulative corticosteroid dose was 96.7 g.

**Interventions:** Patients were treated with oral corticosteroids (4.5 mg prednisone equivalent daily) and topical corticosteroids (51% of patients). After the start of therapy, all patients were followed at 2-week intervals. Patients were considered responders if their disease remained stable for 4 months or more. The response rate was 71% (complete remission 33%, partial remission 38%). Disease was determined to be controlled in 96% of patients. The mean duration of response was 12 months. Three patients (11%) required oral corticosteroids; two patients (7%) required local therapy; and three patients (11%) required systemic therapy.

**Conclusion:** The response rate was 71%, with 33% complete remissions and 38% partial remissions. The median response time was 6 months (range, 2-12 months). The disease control rate was 96% (range, 90%-100%). The median time to progression was 12 months (range, 6-18 months). The median duration of response was 12 months (range, 3-24 months). The median survival time was 18 months (range, 6-42 months). The median follow-up time was 24 months (range, 12-36 months).

Cost: $3,570 (60gr tube), keep refrigerated with a shelf life of 90 days.

Topical Chemotherapy in Cutaneous T-cell Lymphoma  
Positive Results of a Randomized, Controlled, Multicenter Trial Testing the Efficacy and Safety of a Novel Mechlorethamine, 0.02%, Gel in Mycosis Fungoides  
Jordi J. Lluch, MD; Maddalena Zinzani, MD; Jean Guillet, MD; Aren C. Ponder, MD; Bruce E. Broder, MD; Pazin, MD; Curtis M. Garmey, MD; Fabrice L. Cazenave, MD; Zane H. Park, MD; Morris, MD; Mark T. Taylor, MD; Carol M. Auclair, MD; Robert K. Kevy, MD; Biedler, MD; Reinprecht, MD; Beer, MD; Avila, MD; Adam, MD; ranges 2013; 151:1-151:154
Phase I trial of Micro Needle Array-Doxorubicin (MNA-D) in Patients With CTC  O Akilov (abstract WCCL 2016)

- Faster results 3.6m vs. 12m
- Complete response 58% vs 50% monotherapy
- Fewer cases of contact dermatitis: 33% vs. ~60%
- Use gloves, wash hands thoroughly
- Avoid direct contact to others.
- Spare skin folds and skin close to mucosa

Consider combination with topical steroids

Arch Dermatol 2005

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Hypermipigmentation is common after HN2 therapy
(baseline and after 12m)

Mustargen hyperpigmentation resolves spontaneously without sequela.
Secondary cancers, comorbidities and mortality associated with nitrogen mustard therapy in patients with mycosis fungoides: a 30-year population-based cohort study

L.M. Orlandi, L. Biagioli, G. Angiolillo, and L. Ferri

Weibull-fitting the Danish inconstant regulates in 107-105 patients with MF from a regional Danish center using nitrogen mustard treatment, with 105 patients from Danish centers not using nitrogen mustard. The two cohorts were compared by Cox regression analysis.

Both overall, secondary cancers were not significantly increased (hazard ratio 1.09, 95% confidence interval [1.04–1.14]) and subgroups showed no significantly increased risk of radiation-induced skin cancers, and general incidence of cancers in the radiography region in the nitrogen mustard-treated cohort. Furthermore, we found no significantly increased risk of any category of comorbidity, including chronic pulmonary disease, in patients treated with nitrogen mustard (OR 1.09, 95% CI 0.87–1.35). However, mortality and non-specific mortality did not significantly differ between the two cohorts.

Topical Carmustine as Monotherapy or as Multimodality Therapy for Folliculotropic Mycosis Fungoides

Kale M. MacArthur, Neha Srikumar, Elton J. Kim, and Abin H. Rosen

- 13 pts FMF 9 treatment refractory (5CR 4PR), 4 treatment naive (3CR, 1PR)
- 9 patients on other systemic therapies
- Top. Carmustine 0.04% ointment
- Deeper penetration & highly alkylating effect
- 2 patients developed telangiectasias
- No myelosuppression noted

Topical retinoids for patch MF?

Phase 1 and 2 Trial of Bexarotene Gel for Skin-Directed Treatment of Patients With Cutaneous T-Cell Lymphoma

-the number of patients evaluated was 100
-the ORR was 50%
-the 2-year ORR was 70%
-the most common side effect was irritation

- FDA approved since 2000
- Cost 60gr tube: 2010 $1686, 2014 $15,000, 2018 up to $30.450
- ORR: 63% CR: 21%, often durable
- Irritation 73%
Other topical retinoids for MF

Tazarotene 0.1% gel for refractory mycosis fungoides lesions: An open-label pilot study

Nahum, A.M., Tarhan, N., Seter, J., Wienther, W. 1, Dinh, H. 1, Perszyk, J. 1 and Hwu, W.H. 1
Inc., Somerville, MA 2004

- Not FDA approved for MF, but included in NCCN guidelines
- 20 patients up to 20% BSA
- Similar response: Tazarotene RR 58%, CR 35% vs. Targretin RR 63%, CR 21%
- Similar Irritation 84% (mild to moderate) vs. Targretin 73%
- Cost of Tazarotene gel $377 (30gr)

When to use topical retinoids in CTCL?

Rarely

- Unpredictable tolerability and effectiveness
- Localized hyperkeratotic lesions in hands or feet
- Limited lesions of follicular MF with alopecia
- In combination with other SDT or phototherapy for recalcitrant lesions
- Longer lasting results as compared to other forms of topical therapy

Syringotropic MF

Syringotropic MF

- Retinoids: a novel HDAC 1, 2, 3, 6 inhibitor topical gel on-going multicenter trial
- Metabolically labile: HDACi activity only confined to skin
- Preliminary data: modest results as monotherapy
- 20/25 Pruritus improved (VAS reduction >30)
- Minimal AE mostly mild skin irritation (6 patients)
- Phase I: rapid improvement within 1 month
Imiquimod 5% cream effective for limited disease:
1. Post-allo-transplant limited recurrence
2. HTLV-1 ATLL papules
3. Low grade CBCL
Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma

Blood 2016

- Molecular CR in 1/10
- Decrease of T cell clone 9/10

Facial and eyelid involvement may benefit from topical tacrolimus or pimecrolimus

- Eyelid sanctuary site in MF, difficult to treat
- More commonly seen in folliculotropic MF
- 78% of patients with eyelid involvement required treatment with combination skin directed therapy and systemic agent

- Tacrolimus Rallis E J Drugs Derm 2006
- Pimecrolimus P Ortiz Romero WCCL 2016 (good response PLCG1 mutations 21%)

CTCL guidelines: T2 (BSA>10%)

For generalized skin involvement (Skin-Generalized)
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard], Carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)
- Total skin electron beam therapy (TSEBT) (12-36 Gy) reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies
Phototherapy: Highest level of satisfaction in MF treatment

MF Demierre et al Cancer Oct 2006

- PUVA 42% 75%
- NB-UVB 33% 66%
- Steroids 75% 65%
- Mustargen 50% 50%
- Bexarotene 10% 42%
- ECP & Interferon <10% 33%
- Methotrexate <10% <25%
- Ontak <3% 9%

Phototherapy for CTCL

- NB-UVB widely available & few side effects
- Few PUVA booths; Shortage of oxpsoralen resolved
- PUVA & NB-UVB equally effective for patch stage
- PUVA more effective for plaque lesions, darker complexion patients, folliculotropic MF
- Maintenance schedule is easier with PUVA
- PUVA is more carcinogenic after long exposure
- Excimer laser (intense NB-UVB) for single lesions

Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium

RE-PUVA (low dose bexarotene or acitretin)
similar response rate, but faster with less Joules

PUVA-Bexarotene (150mg) after 6 weeks treatment
Phototherapy burn, not T4 erythrodermic MF

Recommend antioxidants prior to therapy
Polypodium leucotomos (Helocare)

- Summer phototherapy holidays.
- Check Vit D & encourage sun exposure in patients with dark complexion
- Some natural sun exposure may help, but avoid sunburn and use sunscreens

New Photodynamic therapy trial

- Open label phase 1-2
- Initial study 50% reduction of lesions in 60% pts.
- Hypericin ointment (Solygenix) activated by 530 - 600 nm yellow light
- Binds to phospholipids in cell membranes (ROS)
- Pro-apoptosis and antiproliferative effect on lymphocytes
- Antibacterial, antiviral and non-specific kinase inhibitor
- Non-mutagenic (not intercalate DNA)
- Initial open label study 50% reduction of lesions in 60% pts.
New trends in Radiotherapy for CTCL

• T2 (plaque)/T4: Total skin EB with lower dose (from 35-40 to 12-20 Gy) higher relapse rate, but lower cumulative dose

• T3 (tumor lesions)

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Outcome of Patients Treated With a Single-Fraction Dose of Palliative Radiation for Cutaneous T-Cell Lymphoma
Tanita O. Thomas, MD, PhD,* Priy Agrawal, BA,* Joan Gottlieb, MD, Steven T. Rosen, MD, Alfred W. Bodnerauer, PhD, Christiane Querfeld, MD, PhD,* John F. Hayes, MD,* Timothy H. Kuzel, MD,* and Bharat B. Mittal, MD* Int J Rad Onc 2012

7-8 Gy in 1-2 fractions
CR 97% (255 T/58 pts.)

Low-dose high dose rate brachytherapy in the treatment of facial lesions of cutaneous T-cell lymphoma
Jameelah S. Mustafa, MD,* Shu-Chen Chou, MD,* John B. Mylonas, MD,* Karen G. Pavuk, BA, Gretchen L. Haines, MD,* and Philip A. Paster, MD* JAAD 2012

Brachytherapy for face or hand/feet MF 4Gy x2
Mostly CR
Source near the tumor with less secondary effect
Mold ideal for convex surfaces with uniform delivery

Folliculotropic MF does not respond well to topical monotherapy

• Localized indolent: steroid foams, retinoids, imiquimod, mustargen, carmustine, excimer UVB, electron beam

• Extensive/aggressive: PUVA or UVA1 combined with low dose oral retinoids or Interferon (α > γ) TIW

• Infection control (bleach baths, hibiclen soaks, antibiotics, etc.)

• Consider localized or total skin EB radiation therapy
Treatment options for lymphomatoid papulosis

• Observation if limited
• Topical therapy (steroids IL, imiquimod, mustargen, bexarotene gel)
• Low dose oral methotrexate
• Phototherapy (UVB, PUVA)

Thank you!
j.guitart@northwestern.edu