Singapore General Hospital
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Cutaneous treatment options for T cell lymphoma

Focus on Mycosis Fungoides

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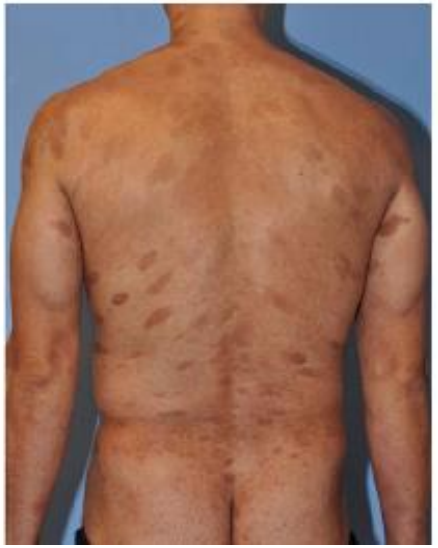
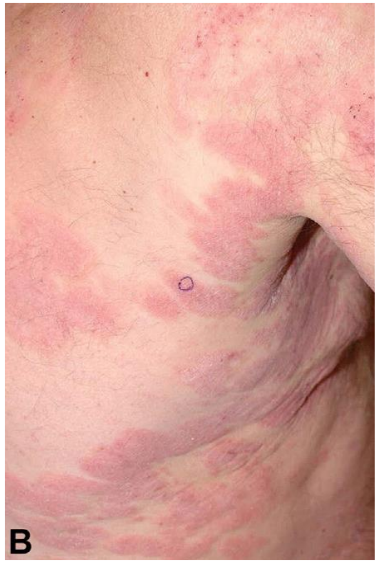
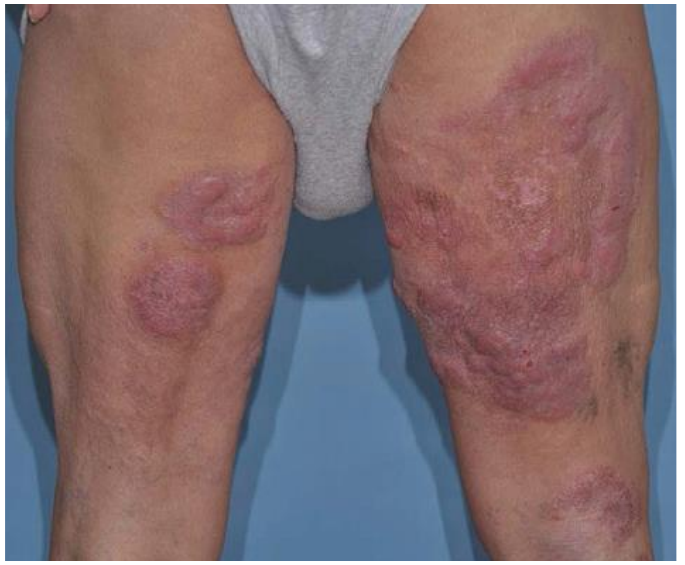
Introduction

- Mycosis fungoides is the most common subtype of CTCL







- Most patients with early stage MF exhibit an indolent clinical course with intermittent, stable or slow progression of lesions
- Patch/ Plaque/Tumour stages

Management considerations in MF

- Most treatments do not result in durable remissions off treatment
- Maintenance/intermittent treatment is often required
- Management in early stages involves skin-directed therapies (SDTs) to:
  - Achieve disease and symptom control
  - Alleviate symptoms
  - Enhance QOL
- Need for treatment regimens that can be tolerated for a long duration with low cumulative toxicity

- Systemic treatment may be combined with SDTs to maximize clinical responses without cumulative toxicity

Tota M et al. Skin-Directed Therapies in Mycosis Fungoides: An Update. Dermatol Ther (Heidelb). 2025 Aug 14
NCCN Clinical Practice Guidelines Primary Cutaneous Lymphoma V3.2025

Role of skin directed therapy

1. First line in stages IA, IB and IIA MF
2. Adjunctive/ supportive treatment in all other stages
3. May be used for maintenance after remission

Table 5a

Recommendations for first-line treatment of MF stages IA, IB, and IIA.

Expectant policy (mainly T1a)		level 4
SDT	Topical corticosteroids (mainly T1a and T2a)	level 3
	Topical chlormethine	level 2
	nbUVB (mainly T1a and T2a)	level 2
	PUVA*	level 2
	Localised RT (for localised MF including pagetoid reticulosis)	level 4

MF, mycosis fungoides; SDT, skin-directed therapy.

* See text for details onrecommendations as to the use of oral, topical, and bath PUVA.

Table 10

Agents that can be used for maintenance after remission has been achieved in MF and SS*.

ECP
IFN-α**
Low-dose methotrexate
nbUVB
PUVA
Retinoids***
Topical chlormethine
Topical corticosteroids

EORTC Recommendations 2023

European Journal of Cancer 195 (2023) 113343

Cutaneous treatment options for CTCL

- Skin direct therapies:
    1. Topical treatment
    2. Light-based therapies
    3. Radiotherapy

- Individualized based on:
    1. Extent of involvement – BSA/thickness of lesions
    2. Patient preference
    3. Tolerability
    4. Comorbidities

Topical therapies

Topical corticosteroids

- Widely used topical anti-inflammatory
- Mechanism: Induce apoptosis, reduce lymphocyte adhesions and suppress cytokine production
- Usually **high-potency topical steroid ointments e.g. clobetasol**
- Lower potency for thin skin areas e.g. face/flexures

Potency	Location	Examples
Low	Face/flexures	Hydrocortisone 1% cream Betamethasone valerate 0.025% cream Desonide cream
Moderate	Body/Limbs	Betamethasone valerate 0.1% Mometasone cream
Potent	Palms/Soles Thick lesions	Bet diproprionate Clobetasol Priopionate

Topical corticosteroids

- Efficacy as monotherapy:
  - Stage Ia: early patch/ plaque stage ORR 75-91%
  - Stage Ib: ORR 62-80%
  - Stage IIb: ORR 33.3%
  - Advanced stage: little to no efficacy
- May be adjunctive at any stage
- May reduce erythema, scaling and pruritis

- Limitation:
- Sustained response is usually not seen after discontinuation
- Risks of long term use – skin atrophy, hypopigmentation, striae and potential systemic absorption

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Jawed SI et al. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part II. Prognosis, management, and future directions. J Am Acad Dermatol. 2014 Feb;70(2):223.e1-17

Topical retinoids

- Retinoids: a group of compounds derived from Vitamin A
- Mechanism: Activates RAR/RXR – modulates cellular differentiation, proliferation and apoptosis
- Limited local availability

- Topical **tazarotene gel**
- Topical **bexarotene 1% gel** (FDA approved for early stage MF)
- Topical tretinoin cream

- Efficacy:
  - Limited evidence, CR 10-60% in 1 study
  - Phase 3 study on Bexarotene gel: 54% CR +PR
- ADR: irritant dermatitis , pruritic, pain

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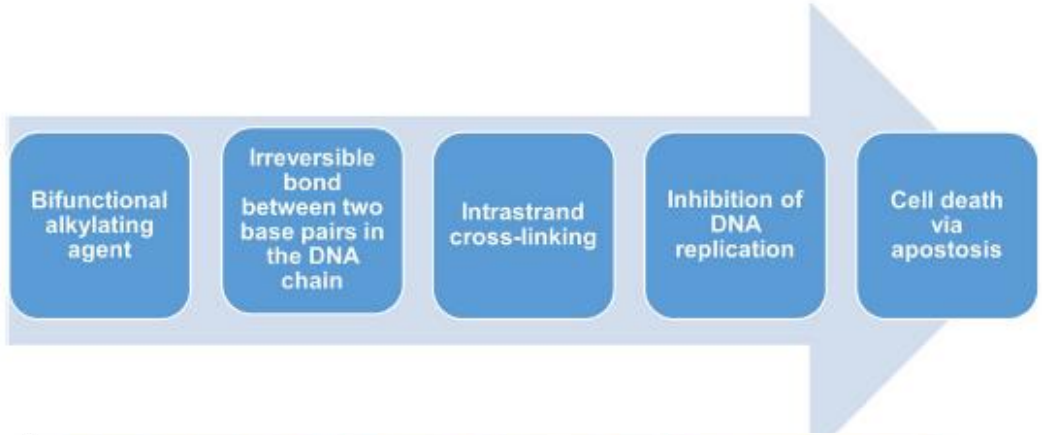
Topical alkylating agents

- Topical **Mechlorethamine** (Nitrogen mustard)
- Topical **Carmustine** (BNCU)
- Limited availability locally



- NM FDA approved 2013 for Stage 1a and 1b MF
- Efficacy:
  - Chlormethine gel ORR 58.5%-83% for early Stage MF
  - Carmustine: ORR 55-80%
  - Occasional long term remissions > 8 years
  - May require 6 months -> maintenance therapy
- ADR:
  - Teratogenic: Not for pregnant/breastfeeding
  - Irritant contact dermatitis – consider concurrent use of topical steroid ointment, does not affect efficacy
  - Carmustine: Risk of systemic absorption – limit to BSA <10% and monitor FBC for myelosuppression

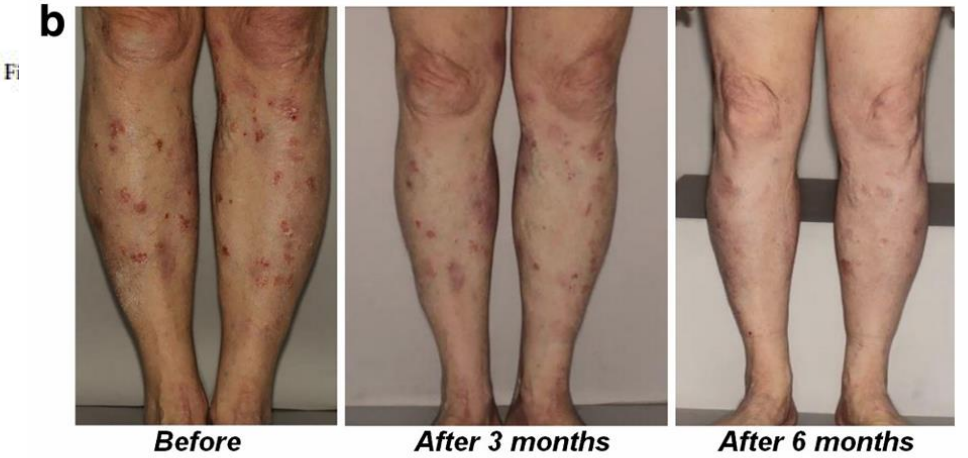


Fig. 1 Patient case images. **a** Epidermotropism and atypical lymphocytes, diagnostic of mycosis fungoides. **b** Skin lesions on the patient's legs before and after 3 and 6 months of once-daily chlormethine gel application

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Dermatol Ther (Heidelb) (2021) 11:1085–1106

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Topical Imiquimod

- Mechanism: Immunomodulator with anti-viral and anti-tumour effects
  - Activates TLR7 inducing pro-inflammatory cytokines IFNα, IFNγ and IL-12
  - Suppresses anti-apoptotic protein Bcl-2 –anti-tumour effects

- Efficacy:
  - Case reports/small studies of efficacy for treating individual lesions
  - CR 45%, PR 35%, NR 20% when applied 5-7 days/week (n=20)

- ADR: Irritant Contact Dermatitis, reports of aching/flu-like symptoms due to acute inflammatory reaction

- In trials: Resiquimod (TLR7/8)

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Light-based Therapies

Phototherapy

- Refers to the use of (Ultraviolet) light in the treatment of diseases

- 2 main modalities:
- **Narrowband UVB (NBUVB)**
- **Psoralen + UVA (PUVA)**
  - Oral PUVA
  - Topical PUVA – Bath, Soak, Paint

- PUVA – deeper penetration, better for thicker lesions

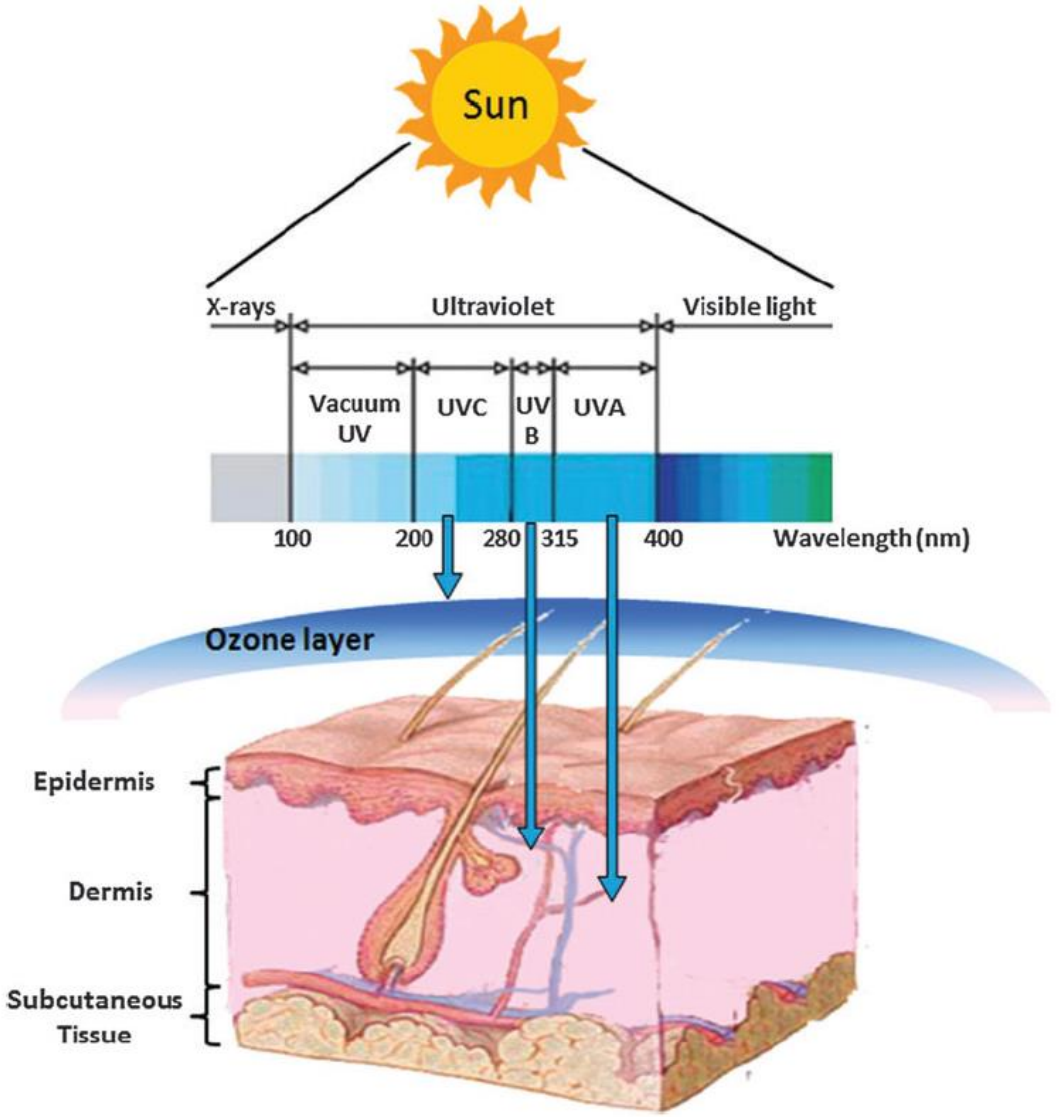

Figure 1. Spectrum of ultraviolet (UV) light and wavelength-dependent penetration of UV in the skin. Highly energetic UVC is nearly completely blocked by the ozone layer. The depth of the penetration through the epidermal layers increases with wavelength since the highly energetic shorter wavelengths are scattered and absorbed to a greater extent. Therefore, UVB mainly reaches the epidermis, while the less energetic UVA rays also affe
To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

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Gupta A et al Ultraviolet Radiation in Wound Care: Sterilization and Stimulation. Adv Wound Care (New Rochelle). 2013 Oct;2(8):422-437

Phototherapy – Mechanism

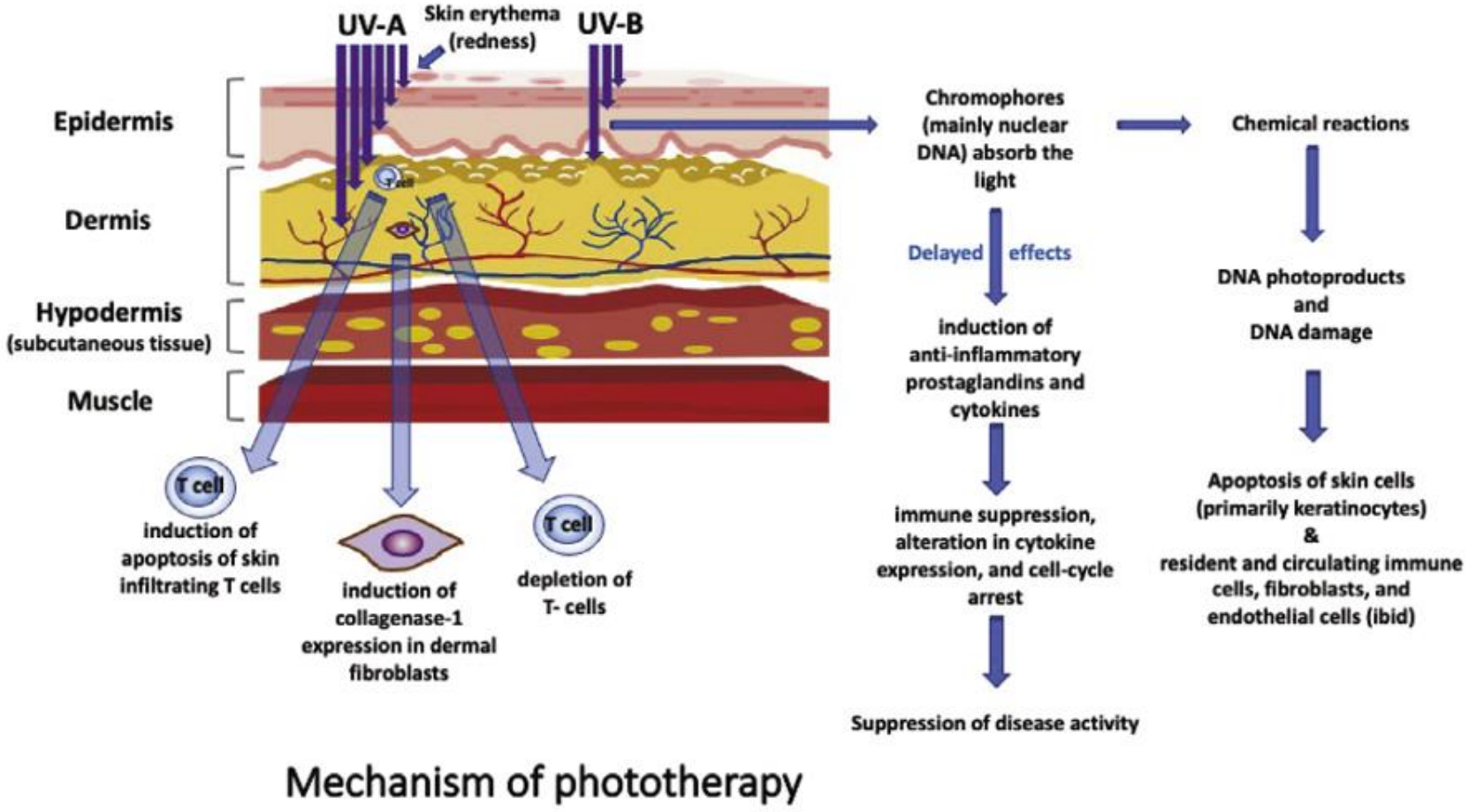

FIG. 1.2 Schematic explanation depicting how phototherapy works.

Photophysics and Nanophysics in Therapeutics 2022, Chap 1: Phototherapy – a critical review

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How is phototherapy done?

- Involves exposing skin to UV in a lighted cubicle
- **2-3 times a week** for the first 2-4 months

- Starting dose depends on skin phototype and is low to avoid sunburn
- Dose gradually increased for better effect as tolerated
- Time to significant improvement: 2-3 months
- Upon achieving clearance, frequency of treatment may be reduced to weekly or fortnightly for maintenance

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NBUVB

- Recommended in Early Stage MF (IA-IIA)
- Esp patch stage/ thin plaques
- Efficacious
  - CR rates 54-90% (average 84%)
  - Patch stage > plaque stage
  - Without maintenance – relapse 29-100% with mean relapse-free interval (RFI) of 5.9-14.5 months
  - With maintenance – relapse rates 4-83% with mean RFI of 3-26 months
- May be combined with retinoids or MTX

Olsen EA et al Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium. J Am Acad Dermatol. 2016 Jan;74(1):27-58.

Possible risks of NBUVB

- Common and short term:
  - Tanning
  - Itch
  - Sunburn
- Long term:
  - Cumulative risks of photocarcinogenesis
  - Premature photoaging
  - Pigmentation

- Not suitable if:
  - Unable to stand/ fall risk
  - Photosensitive conditions/medications
  - History of skin cancers e.g. melanoma/NMSC

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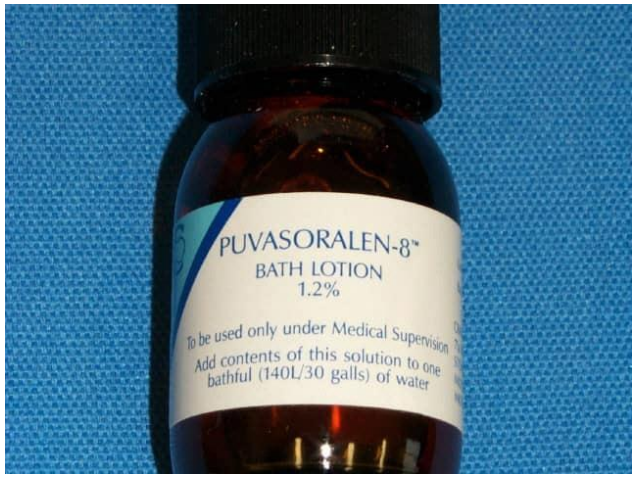
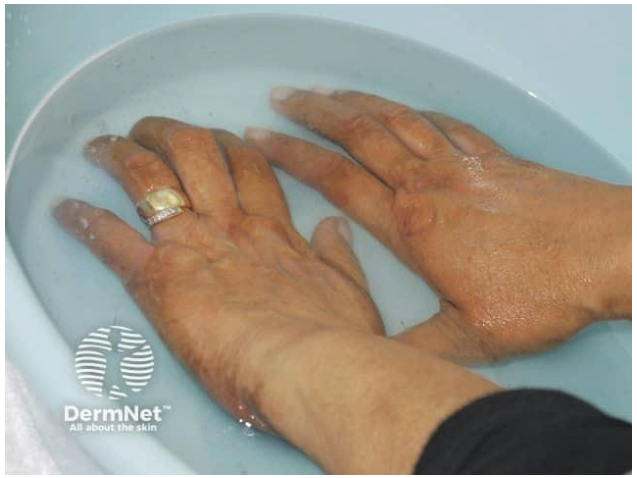
PUVA

- Utilizes UVA in combination with a photosensitizer
  - Oral: 8-methoxypsoralen
  - Topical: Bath/soak/paint

- Deeper penetration than UVB
  - More effective for thick plaques/FMF
  - Higher complete response and relapse-free interval
- However,
  - Increased risk of non-melanoma skin cancers esp > 350 treatments
  - Risks of oral psoralen





Photos from Dermatology. Bolognia 3rd Edition and Dermnet

Risks of Oral PUVA

- Psoralen (Photo sensitizer) taken 2 hours before UVA

- Nausea 10%, headache, dizziness, fatigue, liver toxicity
- Photosensitivity (skin + eyes)
  - Minimize further UV exposure for 24 hours after taking psoralen
    - Avoid outdoor activities
    - Use sunblock
    - Wear long sleeves/ UV protective clothing
    - Use umbrella when outdoors
    - Wear protective sunglasses with a UV400 label (blocks out wavelengths below 400nm)
    - Sunglasses should be worn even inside the car and inside a building if it has glass windows
- Contraindicated in pregnancy and lactation

PUVA combinations

- May be combined with
  - Retinoids – isotretinoin/acitretin/bexarotene
  - IFN-α
  - ECP +IFN/bexatorotene

- Not recommended with
  - MTX – higher risk of photocarcinogensis

- Adjuvant role after TSEBT
  - Improvement in 5 year disease free interval for T1/T2 MF treated with TSEBT followed PUVA maintenance

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Photodynamic therapy

- Application of topical photosensitizer MAL (methyl-aminolevulinic acid) -> activation by light
- Induces a photodynamic reaction, generating ROS
- Direct tumour cell cytotoxicity, destruction of tumour vasculature and immune stimulation

- Early stage MF (patches/plaques)
- Unilesional, few lesions
- Case reports/small series:
  - 50% CR but 42% developed lesions in other areas
- ADR:
  - Pain, erythema, swelling, itch, post inflammatory hyperpigmentation

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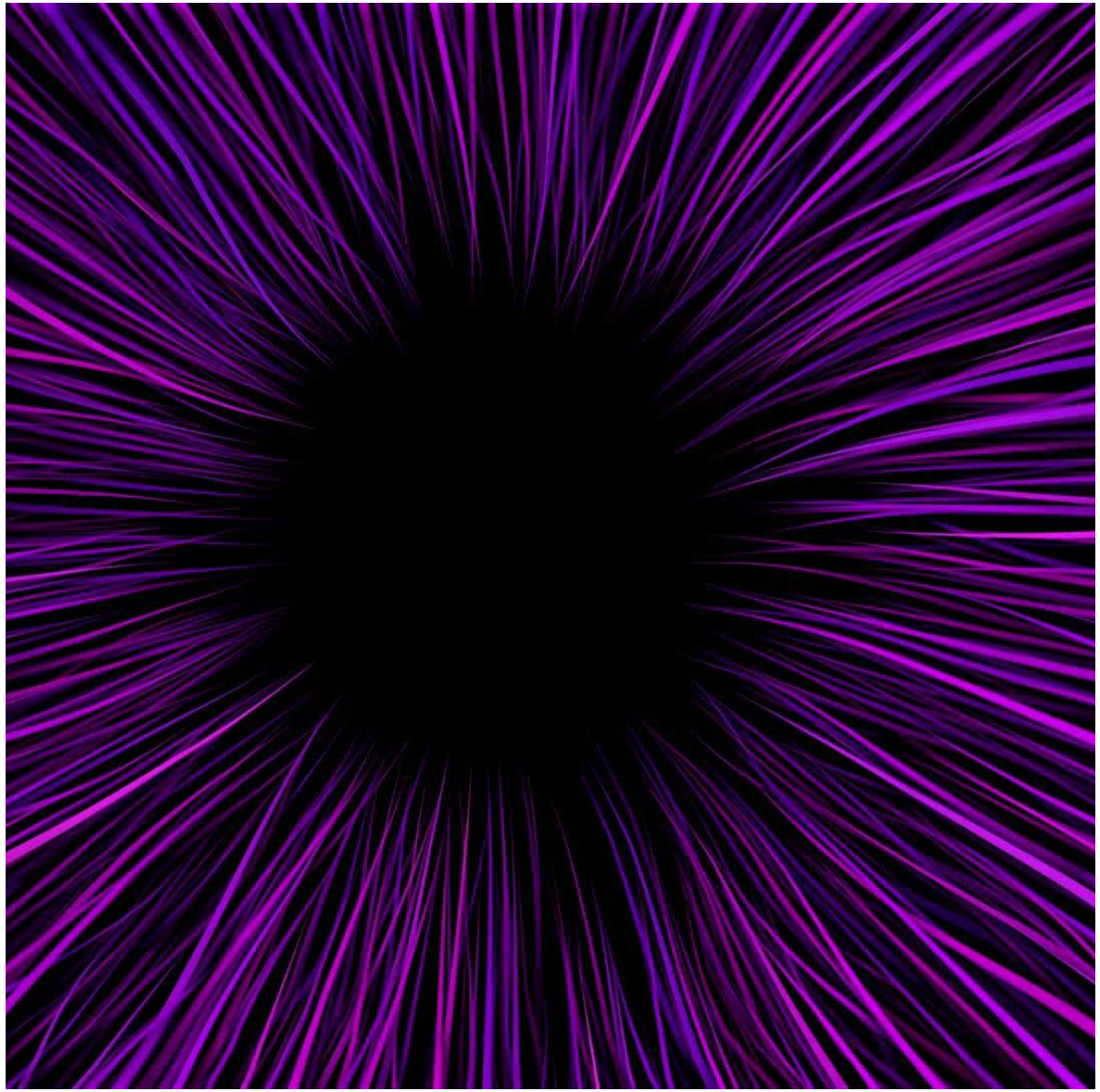
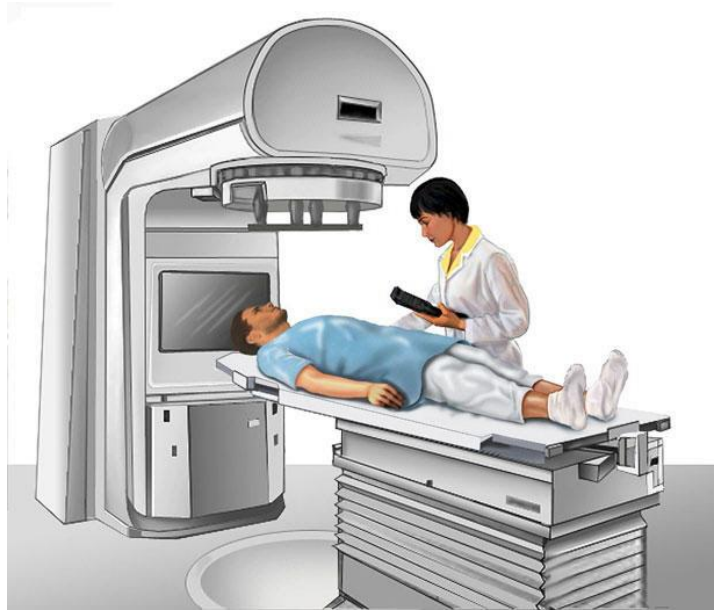
Radiotherapy



Localized Radiotherapy



- MF is highly radiosensitive
- Effective for localized tumours with a CRR of > 90%
- Including special sites e.g. face/genitalia
- Low dose regimens may allow areas to be retreated
- May be combined with other skin directed and systemic therapies

- Higher chance of ablation of malignant T cell clone at treated sites when compared to topical steroids.

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Total Skin Electron Beam Therapy

- Ionizing radiation attenuated to penetrate the skin but avoid toxicity to internal organs e.g. bone marrow
- Used to target the whole body surface = useful when a significant area of body is affected
- Traditionally high dose regimens of 30-36Gy over 8-10 weeks
- Now low dose regimens used e.g. 12Gy in 8 fractions over 2 weeks – comparable efficacy with reduced toxicity
  - UK prospective study: Stage IB-IV MF
  - CR 18%, PR 69%, SD 8%
  - Median response duration 11.8months
  - Median progression free survival: IB 26.5m, IIB 11.3m, III 10.2m
- Risks:
  - Radiation dermatitis
  - Ulceration and poor wound healing
  - Skin carcinogenicity esp with young patients in early stage disease and long life expectancy
  - Alopecia – 100% with high dose, 44% with low dose

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Choice of skin directed therapy

- Considerations:

1. Extent of involvement Localized vs Generalized
2. Thickness of lesions: Patch/plaque/tumour
3. Location of lesions
4. Patient preference and tolerability
5. Comorbidities

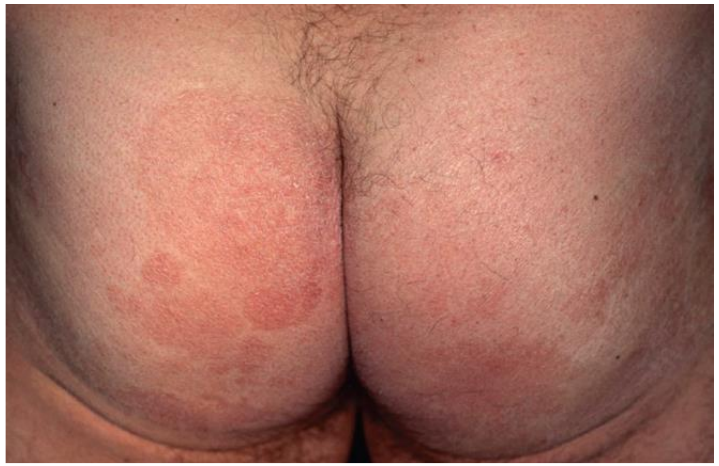
- Combination therapy

- NBUVB may be combined with Retinoids and MTX
- PUVA may be combined with Retinoids and IFN-α

Approach

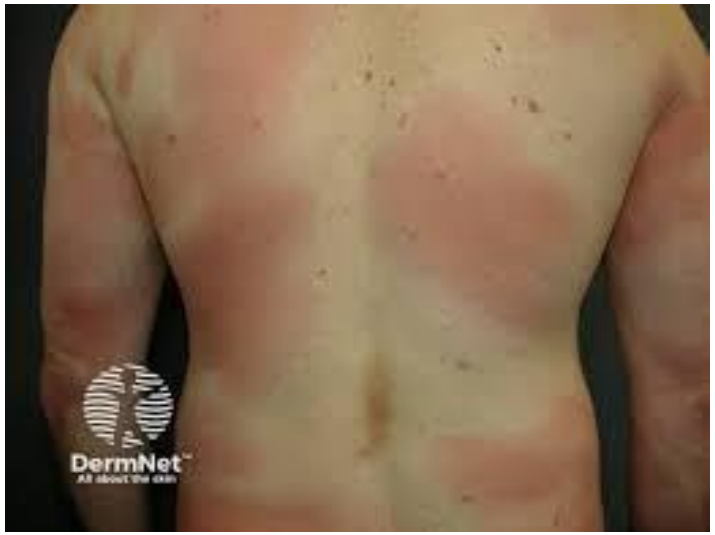
- Localized
  - Patch/thin plaque – topical treatment, localized NBUVB
  - Thick plaque – paint PUVA, RT
  - Tumour – RT

- Generalized
  - Patch/thin plaque – NBUVB -> PUVA
  - Thick plaque – Oral PUVA – usually + retinoid
  - Few Tumours – Localized RT -> maintenance Oral PUVA + retinoid
  - Many Tumours - TSEBT -> maintenance Oral PUVA + retinoid



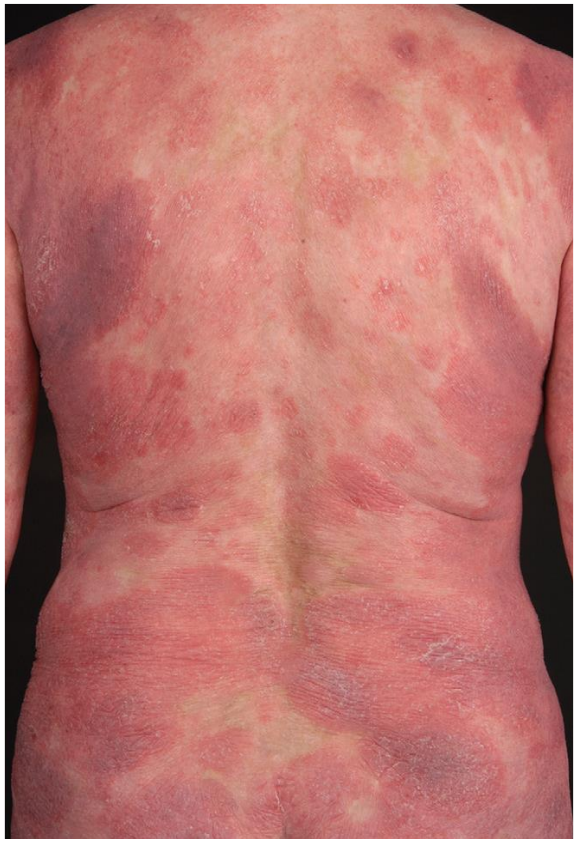
- Localized patch stage

- Topicals
- NBUVB



- Generalized patch stage

- NBUVB
- Topicals adjunctive



- Generalized plaque stage (thick plaques)

- Oral PUVA
- Likely will need retinoid

Skin care

1. General Skincare
2. Management of Pruritis
3. Prevention of Infection

General Skincare

Cleansing	Moisturizing	Treatment	Sun protection
Bathe with lukewarm water Gentle soap-free cleansers	Use of fragrance free moisturizing creams	Topical treatments if needed	Use Sunscreen SPF >30 broad spectrum, sunprotective clothing

Pruritis in CTCL

- Common and may be debilitating
- May not respond completely to standard antihistamines
- Management of CTCL related pruritis:
  - Gabapentinoids
  - Mirtazapine
  - Aprepitant
  - Naltrexone
  - Phototherapy

Table II. Summary of itch-targeted therapies in cutaneous T-cell lymphoma

Drug	Dosage	Mechanism of action in itch relief
Aprepitant	80 mg PO daily or 125 mg PO on day 1, 80 mg PO on days 2-3 given for 3 consecutive days every 2 wk	NK-1-receptor antagonist
Naloxone	0.2 mg SQ qHS then q 3-4 h as needed	μ-Opioid receptor antagonist
Naltrexone	50-100 mg PO daily	μ-Opioid receptor antagonist
Butorphanol	1 mg Intranasal daily	μ-Opioid receptor antagonist κ-Opioid receptor agonist
Mirtazapine	7.5-15 mg PO qHS	Uncertain; adrenergic (α2-autoreceptor, α2-heteroreceptor), serotonergic (5HT-2, 5HT-3), and H1 receptor blockade
Gabapentin	Start 300 mg PO qHS (increase as needed not to exceed 2400 mg daily)	Binds to voltage-dependent $Ca2^+$ channel on nerves, blocks $Ca2^+$ influx, and prevents release of neurotransmitters
Thalidomide	Can start between 50 and 100 mg PO per day and then can increase to 100 mg daily if patient is able to tolerate	Uncertain; stimulates cytotoxic $CD8^+$ T cells and natural killer cells; inhibits production of TNF-alfa, IL-1β, IL-6, GM-CSF; stimulates production of IL-2, IFN-γ

GM-CSF, Granulocyte-macrophage colony-stimulating factor; *IFN*, interferon; *IL*, interleukin; *NK*, n bedtime; *SQ*, subcutaneous; *TNF*, tumor necrosis factor.

J Am Acad Dermatol 2012;67:760-8

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Prevention of infection

- Esp extensive/advanced disease
- Risk of Staph/ HSV infection

- Optimize skin barrier with emollients
- Clearance of staph carriage
- HSV prophylaxis if recurrent HSV

Summary

- Skin directed treatments play an important role in the management of MF
- Early stages
  - Treatment with minimal systemic toxicity
- Advanced stages
  - Adjunct to systemic treatment
  - Maintenance
  - Alleviation of cutaneous symptoms
- Importance of a Multidisciplinary team

Thank You

MultiD Cutaneous lymphoma Clinic – SGH SOC J Wed AM
9.30-12pm
Email: yeo.yi.wei@singhealth.com.sg