Modern management of cutaneous graft-versus-host disease

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Overview

• Acute cutaneous GVHD

• Chronic cutaneous GVHD

• Practical tips for management from a Dermatologist’s perspective
Background

- Graft-versus-host disease is major cause of morbidity and mortality in allogeneic stem cell transplantation
- Commonest affected organs are skin and oral mucosa
- Multidisciplinary input is recommended
- Evidence limited

- Dedicated GVHD clinic* - 13/30 referrals to Dermatology
- Dedicated dermatology input in the Oxford Bone Marrow Transplant clinic provides a one-stop service for up to 40% patients presenting with skin problems
  (Matin et al. submitted to Br J Dermatol)

Acute GVHD

- **Skin**
  - Painful (burning) >>>>> Itchy
  - Rash affecting palms and soles

- **GI tract**

- **Liver**
Acute GVHD

• Skin
  – Painful (burning) >>>> Itchy
  – Rash affecting palms and soles
  – Face – pinnae, cheeks, neck
  – Rapid spread to rest of body esp upper back
  – Scalp usually spared

• GI tract

• Liver
- Subtle erythema (trunk) ➔ oedema
- Morbilliform (macular coalescing – ‘measles like’) rash
- Assess extent
  > 50% BSA topical Rx alone unlikely to help
- Blistering / erosions
- Mucosal involvement – eyes / mouth / genital
Management

- Exclude drug cause
- Consider skin biopsy
- Systemic assessment
  - Temp (falsely normal) – cold / shivering
  - Tachycardia
  - Monitor fluid balance
    - 5l fluid lost through skin if 50% skin involved
- Air mattress (low pressure)
- Treat pain
- Nutritional support
- Sedating anti-histamines
  - Atarax (Hydroxyzine) 10 - 25 mg BD
- High dose oral steroids
- Second line therapies
Management: Emollients

- Symptomatic relief
  - Very dry / scaly
    - 50:50 white soft paraffin: liquid paraffin (WSP:LP)
    - EMOLLIN SPRAY (if blistering)
    - EPADERM / HYDROMOL cream or ointment
  - Dry or very red skin
    - CETRABEN CREAM
    - DOUBLEBASE GEL (greasy)
    - DIPROBASE CREAM (thinner so preferred by males)

Prescribe 500g tubs
Specify formulation – cream vs ointment
Apply up to 2 hourly all over including face and scalp
Hydrocortisone

Eumovate (clobetasone) ointment

Betnovate ointment

Dermovate (clobetasol) ointment / Elocon (mometasone) ointment

Face / Neck / Genitals
30 g tubes

Body
100g tubes

Seek Dermatologist advice

Topical steroid potency ladder
Chronic GVHD

- Skin (75 – 100%)
  - Nails
  - Hair
- Oral mucosa (80–100%)
- Liver
- Eyes
- GI tract
- Lung
- Genitalia
- Joints / fascia
- Haematopoietic / immune

- Skin disease
  - Photosensitivity
  - Wide range of phenotypes
  - Evolution from one form to another
  - Co-existing types
  - Can be the predominant / most symptomatic site of GVHD
Chronic cutaneous GVHD

Clinical findings

- Xerosis / ichthyosis
- Keratosis pilaris-like
- Lichen planus-like (lichenoid)
- Poikiloderma
- Dyspigmentation
- Acral erythema
- Morphoea / Sclerodermatoid

Description

- Dry skin
- Follicular prominence, perifollicular erythema, ‘hedgehog’
- Purple / hyperpigmented papules / plaques
- Telangiectasia + dyspigmentation + epidermal atrophy
- Post-inflammatory hyperpigmentation or vitiligo-like hypopigmentation
- Erythema, oedema, Pain +/- hyperkeratosis
- Superficial or deep sclerotic patches / plaques
ICTHYOSIS ‘fish scale’

Reduced sweating
Itch
Painful ‘cracks’ in skin
# Chronic cutaneous GVHD

## Clinical findings

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KERATOSIS PILARIS

Follicular accentuation
EMOLLIENTS CONTAINING UREA / SALICYLIC ACID

EUCERIN 10% LOTION
HYDROMOL INTENSIVE CREAM
FLEXITOL
CALMURID CREAM
Chronic cutaneous GVHD

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Poikiloderma

Dyspigmentation
Atrophy
Telangiectasia
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Sclerodermoid disease

- Superficial (morphoea-like) – skin feels normal but may be grey / discoloured +/- scaly
- Deep (scleroderma-like) – skin feels very thick

- Rippling
- Change in texture of skin
- Whole body oedema
Sclerodermoid disease

- Superficial (morphoea-like) – skin feels normal but may be grey / discoloured +/- scaly
- Deep (scleroderma-like) – skin feels very thick
- Isomorphic response
  - Localised to sites of minor skin injury or pressure e.g. waistband
- Isotopic response
  - At sites of previous skin damage e.g. varicella zoster
  - Long line sites
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- **Blistering / ulcers (active disease)** – ‘punched out’
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- Blistering / ulcers (active disease) – ‘punched out’
- Alopecia
- Nail changes
- Sclerotic disease (skin tightening) over joints limit movement
Management

- **Photoprotection**
- **Topicals**
  - Emollients
  - Soap substitutes
  - Potent topical steroids
  - Protopic ointment 0.1% (tacrolimus)
- **Phototherapy**
  - Narrowband UVB
  - PUVA (psoralen + UVA)
  - UVA-1
- **Extracorporeal photopheresis (ECP)**

- **Systemic treatments**
  - Prednisolone 1mg/kg
  - Ciclosporin
  - Tacrolimus
  - Mycophenolate mofetil
  - Sirolimus
  - Imatinib
  - Rituximab
  - Etanercept / Infliximab
  - Pentostatin
  - Alefacept
  - Ruxolitinib
    - Topical Ruxolitinib – inhibits donor T cell infiltration in mice models of cutaneous GVHD but preserves follicular stem cells (Takahashi 2016)
Photoprotection

- UV light exposure can trigger GVHD and can prolong / worsen cutaneous GVHD
- Phototoxic drug eruptions e.g. voriconazole, NSAIDs
- Increased risk of UV-induced skin cancers*

Advice should include:
- Avoid peak hours of sunshine (11am – 3pm)
- Broad spectrum sunscreen (SPF 30+) regularly
- Use broad-brimmed hats, long sleeves, trousers or UV-protective clothing (physical methods more effective than sunscreens)

*DePry JL et al. JAMA Dermatol. 2015 Jul;151(7):775-82
Tips for topical treatments

• Always prescribe soap substitutes and emollients
• Prescribe largest quantities – 500g or 100g
• Leave 20 min gap between applying emollient and steroid
• Potency of topical steroid depends on site
• Apply steroids once daily – generously!
• Explain / show what to do

Cosmetic camouflage

www.changingfaces.org.uk
Phototherapy

- No RCT evidence
- No guidelines on dosing / frequency
- Targets skin disease but mechanism of action unclear
  - Apoptosis
  - Anti-proliferative effects
  - Local immunosuppression
  - Immunomodulation

!! Photosensitising drugs
!! Balance with skin cancer risk

- Narrowband UVB (311nm)
  - Three x weekly
  - Superficial disease, lichenoid subtype
  - CRR 75% (n=15)

- Psoralen + UVA (PUVA) (320nm)
  - Twice weekly
  - Improvement after 10 Rx
  - Max response after 15 sessions
  - CRR ~ 40% (n=54)

- UVA-1 (340nm)
  - Few centres in UK
  - CRR ~ 60% (n=24)

Kroft EBM et al JAAD 2008; 59: 1017
York NR et al Int J Derm 2010; 49: 623
Garbutcheon-Singh KB et al Aust J Dermatol 2015; 56: 93
When to refer to a Dermatologist:

- Diagnosis is not clear e.g. drug eruption versus GVHD or suspect alternative skin condition
- Skin disease unresponsive to potent topical steroids for > 3 weeks
- Topical calcineurin inhibitors (tacrolimus or pimecrolimus) (Choi CJ Arch Dermatol 2001; 137: 1202)
- Early superficial / evolving sclerodermoid skin disease
- Suspected new skin cancer
- Skin ulceration
- Skin disease significantly impacting on quality of life
Summary

• Encourage all patients to photoprotect

• Subtle erythema in darker skin types – scaling and dyspigmentation are indicators – biopsy to assess for active GVHD

• Consider alternative common skin conditions e.g seborrhoeic dermatitis

• Whole body oedema / rippling of skin can be an early sign of evolving sclerodermatoid cGVHD

• Engage with your local Dermatologists!
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