MANAGEMENT OF CUTANEOUS LYMPHOMAS AND CHRONIC GVHD

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GVHD

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Disclosures

• **Speakers’ bureau**
  - Spectrum
  - Seattle Genetics
  - Celgene

• **Advisory boards**
  - Celgene
  - Spectrum
OBJECTIVES

Classification of GVHD
Pathophysiology of GVHD
Risk factors for GVHD
Clinical features of ch GVHD
Treatment outline for GVHD
WHAT IS A HEMATOPOEITIC STEM CELL?

- Ability to provide life long hematopoiesis of all blood-cell lineages after transplantation into lethally irradiated recipients.
THERAPEUTIC PRINCIPLES BY ALLOGENEIC SCT

- Ablation of host hematopoiesis, normal and malignant or immunosuppression of host immunity to allow engraftment
- Re-establishment of donor hematopoiesis
- Donor immune reconstitution (donor derived)
- Donor anti-tumor effect (GVL)
MAJOR COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

- Acute graft versus host disease (GVHD)
  Skin, liver, gastrointestinal tract

- Chronic graft vs host disease
  Skin, mucous membranes, liver, lung

- All patients require immunosuppression or T cell depletion-risk of infection, relapse

- Incidence of grade II-IV GVHD: 10-40%

- Incidence of ch GVHD- 60-80%
PATHOGENESIS

Criteria for the development of GVHD are:

- The graft must contain immunologically competent cells.
- The host must possess important transplantation alloantigens that are lacking in the donor graft, so that the host appears foreign to the graft, and is, therefore, capable of stimulating it antigenically.
- The host itself must be incapable of mounting an effective immunological reaction against the graft, at least for sufficient time for the latter to manifest its immunological capabilities; that is, it must have the security of tenure.

ININCIDENCE OF GRAFT VS HOST DISEASE

Acute GVHD

Days after HCT

Probability

Grade II 31%

Grades III-IV 15%
Cumulative probability of grade II–IV acute graft-vs.-host disease (GVHD) after allogeneic bone marrow transplantation (BMT) from a genotypically human leukocyte antigen (HLA) identical sibling or other family members mismatched for 0–3 loci on the non-shared haplotype.
Risk factors for GVHD

- Higher degree of HLA mismatching
- Older age of donor and/or recipient
- Donor and recipient gender disparity (female donor to male recipient)
- Alloimmunization of the donor (history of pregnancy, transfusions)
- Source of stem cells (peripheral blood precursor cells [PBPC] rather than bone marrow or umbilical cord blood)
- Prior acute GVHD
- Administration of unirradiated donor buffy coat transfusions (e.g., donor lymphocyte infusions)
- Previous splenectomy
- Cytomegalovirus seropositivity (donor and/or recipient)
- Donor Epstein-Barr virus seropositivity
Classification of GVHD

• **Classic acute GVHD** – Cases present within 100 days of hematopoietic cell transplant (HCT) and display features of acute GVHD. Features of chronic GVHD are absent.

• **Persistent, recurrent, late onset acute GVHD** – Cases present greater than 100 days post-HCT with features of acute GVHD. Features of chronic GVHD are absent.

• **Classic chronic GVHD** – Cases may present at any time post-HCT. Features of chronic GVHD are present. There are no features of acute GVHD.

• **Overlap syndrome** – Cases may present at any time post-HCT with features of both chronic GVHD and acute GVHD.
Clinical features of chronic GVHD

- Skin – 67 percent
- Mouth – 60 percent
- Liver – 52 percent
- Lung – 50 percent
- Eye – 48 percent
- Joints and fascia – 48 percent
- Gastrointestinal tract – 30 percent
- Genitalia – 12 percent
### Diagnosis of ch GVHD

Diagnosis of ch GVHD requires the presence of at least one diagnostic clinical sign of ch GVHD or at least one confirmed biopsy or relevant test. Exclude other diagnosis.

<table>
<thead>
<tr>
<th>Organ or site</th>
<th>Diagnostic (sufficient to establish the diagnosis of chronic GVHD)</th>
<th>Distinctive (seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)</th>
</tr>
</thead>
</table>
| Skin                | • Poliosisderma  
                      • Lichen planus-like features  
                      • Sclerotic features  
                      • Morphea-like features  
                      • Lichen sclerosus-like features                                                    | • Depigmentation                                                                                   |
| Nails               | • Dystrophy  
                      • Longitudinal ridging, splitting, or brittle features  
                      • Onycholysis  
                      • Pterygium unguis  
                      • Nail loss (usually symmetric; affects most nails)**                                  |                                                                                                   |
| Scalp and body hair | • New onset of scarred or nonscarring scalp alopecia (after recovery from chemoradiotherapy)  
                      • Scaling, papulosquamous lesions                                                        |                                                                                                   |
| Mouth               | • Lichen-type features  
                      • Hyperkeratotic plaques  
                      • Restriction of mouth opening from sclerosis                                                  | • Xerostomia  
                      • Mucocele  
                      • Mucoosal atrophy  
                      • Pseudomembranes*  
                      • Ulcers*                                                                                   |
| Eyes                |                                                                                                                                | • New onset dry, gritty, or painful eyes³  
                      • Cicatrinal conjunctivitis  
                      • Keratoconjunctivitis sicca⁴  
                      • Confluent areas of punctate keratopathy                                                     |                                                                                                   |
| Genitalia           | • Lichen planus-like features  
                      • Vaginal scarring or stenosis                                                                   | • Erosions*  
                      • Fissures**  
                      • Ulcers**                                                                                   |
| GI tract            | • Esophageal web  
                      • Strictures or stenosis in the upper to mid third of the esophagus*                          |                                                                                                   |
| Lung                | • Bronchiolitis obliterans diagnosed with lung biopsy                                                                               | • Bronchiolitis obliterans diagnosed with PETs and radiology⁵                                      |
| Muscles, fascia, Joints | • Fascitis  
                      • Joint stiffness or contractures secondary to sclerosis                                      | • Myositis or polymyositis⁶                                                                     |
GRADING OF ch GVHD

NIH consensus criteria for GVHD severity

• **Mild** – Involves two or fewer organs/sites with no clinically significant functional impairment

• **Moderate** – Involves three or more organs/sites with no clinically significant functional impairment or at least one organ/site with clinically significant functional impairment, but no major disability

• **Severe** – Major disability caused by chronic GVHD
PREVENTION OF GVHD

- T cell depletion
- Methotrexate plus calcineurin inhibitor
- Sirolimus + tacrolimus
- Mycophenolate Mofetil
- Combination with Post transplant Cytoxan
- ATG
- Novel approaches like inclusion of ECP, HDACi prior to transplant
GVHD TREATMENT

- Steroids- high dose (most important) topical or systemic
- Calcineurin inhibitors
- Rapimmune
- Mycophenolate Mofetil
- ATG, anti CD3,
- Cytoxan
- Denileukin Diftitox, alemtuzumab, dacluzimab
- JAK/STAT inhibitors
- Immunemodulation
- Mesenchymal stem cells
Chronic GVHD
Symptom Management
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Disclosures

No Disclosures
Objectives

• Identify common presentations of chronic GVHD by body system
• Discuss prevalence of cGVHD in the post allo transplant population
• Review available assessment tools for the cGVHD patient
• Discuss management options including both medical and nursing approaches
Goals of Treatment

- Is there a cure?
- Reduce symptom burden to patient
- Control objective symptoms related to GVHD
- Prevent further damage and resulting disability
- Balance potential toxicity from treatment with actual benefit perceived by the patient
## Realistic Goals: Response to Treatment

### Table 6. Agents used for secondary treatment of chronic GVHD*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Overall response*</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td>65-70</td>
<td>70%-78% at 1 y</td>
</tr>
<tr>
<td>Rituximab</td>
<td>66-86</td>
<td>72% at 1 y</td>
</tr>
<tr>
<td>Imatinib</td>
<td>22-79</td>
<td>75%-84% at 1.5 y</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>53-56</td>
<td>34%-60% at 1-3 y</td>
</tr>
<tr>
<td>Mesenchymal stem cells</td>
<td>50-74</td>
<td>78% at 2 y</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>26-64</td>
<td>67%-96% at 1 y</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>76</td>
<td>72% at 3 y</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>52</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Other therapies summarized in other reviews**
- Calcineurin inhibitor
- High-dose methylprednisolone
- Methotrexate
- Thalidomide
- Hydroxychloroquine
- Clofazimine
- Thoracoabdominal irradiation
- Alefacept
- Infliximab
- Etanercept

mTOR, mammalian target of rapamycin.

*Simplified from Inamoto and Flowers³⁶; see Flowers et al,³⁵ Wolff et al,⁶³ and Flowers and Deeg⁶⁴ for other reviews.

**20%-82% overall response rates reported.
Cutaneous GVHD Presentation and Management

- Seen in approximately 67% of patients
- Dry skin, pruritus, pigment changes, edema, erythema, stippling, lichen planus, hardening of skin, hidebound
- Daily use of emollients for management of dry skin minimizes pruritus and risk for infection-prefer ointment to lotion and cream
- Higher risk for skin cancer (especially SCC)
  - Teach prevention including sun protection and surveillance
- May need hydrocortisone, sarna, or amlactin for pruritus
  - Doxepin, gabapentin, naloxone used for systemic control of itching
  - NBUVB for pruritus, PUVA, ECP
  - Corticosteroid use *
Cutaneous Manifestations
Corticosteroid Choices and Potency

<table>
<thead>
<tr>
<th>Corticosteroid Choice</th>
<th>Potency</th>
<th>Side Effects</th>
<th>Availability</th>
<th>Contraindications</th>
<th>Prescribing Considerations</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone</td>
<td>High</td>
<td>Mild</td>
<td>Oral</td>
<td>None</td>
<td>Short-term</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Medium</td>
<td>Mild</td>
<td>Oral, IM</td>
<td>Cushing's Disease</td>
<td>Short-term</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Medium</td>
<td>Mild</td>
<td>Oral, IM</td>
<td>Cushing's Disease</td>
<td>Short-term</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>Low</td>
<td>Mild</td>
<td>Oral, IM</td>
<td>Cushing's Disease</td>
<td>Short-term</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>Very Low</td>
<td>Mild</td>
<td>Oral, IM</td>
<td>Cushing's Disease</td>
<td>Short-term</td>
<td>1-2 weeks</td>
</tr>
</tbody>
</table>

*Note: Potency is a measure of how effective the corticosteroid is, with high potencies being the most effective. Side effects and other considerations may apply.*
Corticosteroid Topical

- Topical application of corticosteroids may lead to atrophy of treated skin
- Utilization of lower potency (class VI-VII) on face and intertriginous areas recommended
- Aceniform rash, dry scaly eruption with follicular pustules around mouth, rosacea like rash, purpura, hyper/hypo pigmentation
Ulcerations and Infection Risk for Cutaneous GVHD

- Culture and biopsy as appropriate
- Keeping area moist and without fissure
- Minimize colonization with bleach bath
- Engage wound care specialists/plastic surgery as indicated
Ulcerations in cutaneous GVHD
Sclerotic Changes to Skin

- Affected areas can be minimal or diffuse
- Superficial tightening
- Deep sclerotic changes
- Hidebound
- ECP, IL2, Monoclonal antibodies
Physiologic Changes in Cutaneous GVHD

Epidermal inflammation
Physiologic Changes in Cutaneous GVHD

Dermal inflammation
Physiologic Changes in Cutaneous GVHD

Fascial inflammation
Patient Education

• Teaching the patient about signs of progression and/or complication is key
• Tightness- edema vs infiltrative disease mediated by GVHD
• Change in ROM- identify specific activities that patient can be comfortable evaluating
• SOB, decrease in appetite with feeling of bloat, muscle cramping- all more insidious signs of progression
Mucosal Presentation and Management

- Approximately 60% of patients with GVHD
- Xerostomia
  - Biotene products, lemon candy, gum, muscarinic agents (Pilocarpine, cevimeline)
  - Avoid caffeine and alcoholic beverages
- Oral lesions - leukoplakia (cancer vs GVHD), lichenoid, mucoceles, ulcerations, oral candidiasis
  - Surveillance for cancerous lesions (biopsy as needed)
  - Topical dexamethasone, budesonide, tacrolimus, clobetasol, fluocinonide, tacrolimus
    - Apply gel to affected area. No food or drink for 15 minutes. Cover with gauze
    - Topical rinse - 5ml for 5-15 minutes then spit. No food or drink for 15 minutes after
  - Episil
  - Treatment for oral candidiasis (high risk with immunosuppressive therapy and topical corticosteroid)
Mucosal Manifestations
11/4/2016 – while on Dexamethasone swish & spit

1/6/2017 – 6 weeks of Budesonide sol swish & spit for 1 min, TID
Mucosal Management

• Sensitivity to temperature change, spicy food, toothpaste
  – Utilization of children’s toothpaste
  – Episil
  – Minimize consumption of spicy food
  – Appropriate treatment of GVHD
Patient Education

• Oral hygiene is paramount
• Regular dental appointments with a dentist familiar with GVHD
• Signs of worsening of GVHD- increase in symptoms, new lesions, subtle changes
• Surveillance for cancerous lesions
Eye Presentation and Management

- 40-60% of patients with chronic GVHD
- Photophobia and significant pain common
- Cataracts
- Eye drops
- Punctal plugging, prose lenses
- Protective eye wear
- New treatments- Xiidra
Gastrointestinal Presentation and Management

• Approximately 30% of patients
• Esophageal involvement leading to esophageal web and tapering of esophagus
  – Choking on pills/food, weight loss, painful ulcers
  – Encourage fluid with each bite of food/pills
  – GI consult, speech therapy possible esophageal dilatation
  – Nutritionist
• Small and large bowel involvement
  – Loose stools, malabsorption
  – Gastric pain, gastric bloating
  – Anorexia, nausea, vomiting, weight loss
  – Budesonide, carafate, anti-diarrheals, pancreatic enzymes
Liver Manifestations and Management

- 50% of patients will have involvement of the liver
- Abnormal LFTs—elevation alkaline phosphatase, AST, ALT, and bilirubin
- Can mimic other hepatic disease
- Rule out other potential causative factors
- May need to adjust immunosuppression; Actigall
Pulmonary Presentation and Management

- Approximately 50% of patients with GVHD
- Obstructive versus restrictive
- Bronchiolitis obliterans and bronchiolitis obliterans organizing pneumonia
  - Evaluation for shortness of breath
  - PFT
- Assess for subtle signs
  - Chronic dry cough, exercise intolerance, decreased activity
- Overlying infection
- Idiopathic pneumonia syndrome
- Diffuse alveolar hemorrhage
- Management involves identification and reversal of causative factors when possible
  - Pulmonary rehab
  - Immunosuppression therapy
  - Smoking Cessation
Musculoskeletal Presentation and Management

- Up to 50% patients, but often presents months to years after transplant
- Fasciitis- joint mobility limitation often in the continuum of skin findings
- Myositis- weakness with or without myalgia, symmetrical proximal muscles
  - Check serum creatine kinase
- Edema of extremities- generally non-pitting
  - Massage by lymphedema experts
  - Compression stockings
- Muscle atrophy
  - Physical and Occupational therapy to minimize destruction
  - Assess utilization of corticosteroids
- Muscle cramping
  - R/O electrolyte imbalance (calcineurin inhibitors cause hypomagnesemia and hyperkalemia)
  - R/O neuropathy
  - Tonic water
Gynecologic Manifestations and Management

- Exact incidence is unknown
- Reports range between 11-48%
- Often under reported and not assessed
- Vaginal dryness, itching, burning, and pain, loss of libido, inflammation and stenosis
- Diagnostic- lichen planus features, vaginal scarring or stenosis
- Erosions, fissures, and ulcers may occur
- Treatment- hormone replacement, dilators-GYN referral
Other Manifestations

- Recurrent sterile effusions
  - Polyserositis
  - Pericardial effusion
- Renal manifestations
  - Nephrotic syndrome

Any new symptom should be evaluated by hematologist
Assessment Tools

• Need for consistency as many components of assessment are subjective
• Must include both subjective and objective components to be comprehensive
• NIH consensus recommendations 2014
• Paul Carpenter outlines specific GVHD assessment
  – http://www.fhcrc.org/science/clinical/gvhd
Review on Each Visit

Table 3. Chronic GVHD review of systems

<table>
<thead>
<tr>
<th>No.</th>
<th>System/others</th>
<th>Inquire/description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skin</td>
<td>Skin feels tight or hard, increased dryness, pruritus, or looks different (ie, new rash, papules, discoloration, shining scar-like, scaly)?</td>
</tr>
<tr>
<td>2</td>
<td>Sweat glands</td>
<td>Inability to sweat or to keep body warm?</td>
</tr>
<tr>
<td>3</td>
<td>Skin appendages</td>
<td>Loss of hair (scalp or body including bows or lashes), or nail changes (ridges or brittle, loss)?</td>
</tr>
<tr>
<td>4</td>
<td>Fasciae/joints</td>
<td>Stiffness or pain in the wrists, fingers, or other joints?</td>
</tr>
<tr>
<td>5</td>
<td>Eyes</td>
<td>Eye dryness, sensitivity to wind or dry environments (air conditioning), pain?</td>
</tr>
<tr>
<td>6</td>
<td>Mouth</td>
<td>Oral dryness, taste alterations, sensitivities (spicy/carbonate drinks, toothpaste), ulcers/sores, pain?</td>
</tr>
<tr>
<td>7</td>
<td>Esophagus</td>
<td>Foods or pills gets stuck upon swallowing?</td>
</tr>
<tr>
<td>8</td>
<td>Lungs</td>
<td>Cough, dyspnea (on exertion or rest) or wheezes?</td>
</tr>
<tr>
<td>9</td>
<td>Genital tract</td>
<td>Vaginal dryness, pain, dyspareunia (female); pain or dysuria due to stenosis of urethra (male)?</td>
</tr>
<tr>
<td>10</td>
<td>Weight loss</td>
<td>Unexplained weight loss or inability to gain weight (pancreatic insufficiency or hypercatabolism)?</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Frequency of evaluation/monitoring</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Review of systems (see Table 3 for chronic GVHD-specific questions)</strong></td>
<td>Every clinic visit</td>
<td></td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete skin examination (look, touch, pinch)</td>
<td>Every clinic visit</td>
<td></td>
</tr>
<tr>
<td>Oral examination</td>
<td>Every clinic visit</td>
<td></td>
</tr>
<tr>
<td>Range of motion assessment</td>
<td>Every clinic visit</td>
<td></td>
</tr>
<tr>
<td>Performance score</td>
<td>Every clinic visit</td>
<td></td>
</tr>
<tr>
<td><strong>Nurse assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>Every clinic visit</td>
<td></td>
</tr>
<tr>
<td>Height/adults</td>
<td>Yearly</td>
<td></td>
</tr>
<tr>
<td>Height/children</td>
<td>Every 3-12 mo</td>
<td></td>
</tr>
<tr>
<td>Medical photographs</td>
<td>~100 d after HCT (baseline), at initial diagnosis of chronic GVHD, every 6 mo if skin or joints are involved and during treatment until at least 1 y after discontinuation of treatment</td>
<td></td>
</tr>
<tr>
<td>Other evaluations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFTs</td>
<td>~100 d after HCT (baseline); see also Table 4</td>
<td></td>
</tr>
<tr>
<td>Nutritional assessment</td>
<td>As clinically indicated and yearly if receiving corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Physiotherapy with assessment of range of motion</td>
<td>Every 3 mo if sclerotic features affecting range of motion until resolution</td>
<td></td>
</tr>
<tr>
<td>Dental or oral medicine consultation with comprehensive soft and hard tissue examination, culture, biopsy, or photographs of lesions, as clinically indicated</td>
<td>Every 3-6 mo or more often as indicated</td>
<td></td>
</tr>
<tr>
<td>Ophtalmology consultation with Schirmer test, slit-lamp examination, and intraocular pressure</td>
<td>At initial diagnosis and every 3-6 mo or more often as indicated</td>
<td></td>
</tr>
<tr>
<td>Gynecology examination for vulvar or vaginal involvement</td>
<td>Every 6 mo or more often as indicated</td>
<td></td>
</tr>
<tr>
<td>Dermatology consultation with assessment of extent and type of skin involvement, biopsy, or photographs</td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>Neuropsychological testing</td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>Bone mineral assessment (DEXA scan)</td>
<td>Yearly during corticosteroid treatment or if prior test was abnormal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>~100 d after HCT if continuing corticosteroid treatment (baseline)</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Flowers and Vogelsang.69
Summary

• Chronic GVHD manifests differently for individual patients
• Many symptoms are nuanced and require an astute provider/nurse to identify
• Patient education is critical
• Early intervention may prevent permanent disability
• Be Aware. Educate. Act
References

- [www.uptodate.com](www.uptodate.com) Clinical manifestations, diagnosis, and grading of chronic graft vs host disease
- [www.uptodate.com](www.uptodate.com) Treatment of chronic graft versus host disease
Cutaneous Lymphomas

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Director, Cutaneous Lymphoma Program
Disclosures

• Advisory Board
  - MiRagen, Actelion, Celgene, Therakos
• Consultant
  - Mindera
• Investigator
  - Celgene, MiRagen, Trillium Therapeutics, Actelion, Kyowa, Soligenix
Objectives

• Discuss the classification and staging of cutaneous T-cell lymphoma and state the prognosis associated with each stage.
• List and describe the skin-directed and systemic treatment options that are appropriate for each stage and cutaneous manifestation of cutaneous T-cell lymphoma.
• Recognize the impact of disease and disease symptoms on quality of life in patients with CTCL.
• Recognize the major subtypes of cutaneous B cell lymphomas, the clinical features, prognosis, management, and outcome.
### Cutaneous T cell lymphomas

#### Mycosis fungoides
- Folliculotropic type
- Pagetoid reticulosis
- Granulomatous slack skin

#### Sézary syndrome

#### Primary cutaneous CD30+ lymphoproliferative disorders
- Lymphomatoid papulosis (type A-E)
- Primary cutaneous anaplastic large cell lymphoma

#### Subcutaneous panniculitis-like T cell lymphoma

#### Primary cutaneous γδ T cell lymphoma

#### Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma

#### Primary cutaneous acral CD8+ T cell lymphoma

#### CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder

#### Primary cutaneous peripheral T cell lymphoma, NOS

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Swerdlow SH et al. Blood 2016 127:2375-2390
Mycosis Fungoides

- Prototype of CTCL
- Low-grade lymphoma
- Post-thymic T-cell malignancy (CD4+/CD45RO+)
- Malignancy of 3 different T-cell populations:
  - Features of T-regulatory (CD25+FoxP3+), Th2- and Th17-cell phenotype
- **Th2-driven** immunosuppressive properties
  - Secretion of IL-4, IL-5, IL-6, IL-10
  - Peripheral eosinophilia, elevated IgE
  - Decreased antigen-specific T-cell response
  - Impaired cell mediated cytotoxicity
- Patch, plaque, tumors and erythroderma

Berger C et al. 2005; Dummer R et al. 1996; Krejsgaard T et al. 2010
Sézary Syndrome

- Systemic and aggressive variant
- Exfoliative erythroderma
- Ectropion, alopecia, palmoplantar keratoderma
- Severe pruritus
- Circulating, atypical, malignant T-lymphocytes (Sézary cells)
CTCL Staging

All patients
- Physical exam
  - Skin burden, nodes
- Skin biopsy
  - Immunophenotyping
  - TCR analysis
- CBC, CMP, LDH

Selected patients
- Sézary cell counts by flow cytometry
  - CD4+/CD7-; CD4+/CD26-
  - CD4:CD8 ratio
- TCR analysis in PBMCs
- HTLV-1 titer
- PET/CT scans
- Lymph node biopsy
- Bone marrow biopsy
Mycosis Fungoides/Sézary Syndrome

Clinical signs

Skin pathology Laboratory tests

Molecular tests

Prognostication

What are the key prognostic markers that can help guide clinical management of CTCL?
Stage-based Treatment Algorithm for Mycosis Fungoides and Sézary Syndrome

<table>
<thead>
<tr>
<th>Stage</th>
<th>IA</th>
<th>IB/IIA</th>
<th>IIB</th>
<th>IIIA/B</th>
<th>IVA_{1/2}</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patches/Plaques (T_{1/2}N_{0-3}M_{0-5}B_{0-1})</td>
<td>Tumors (T_{3}N_{0-2}M_{0-5}B_{0-1})</td>
<td>Erythroderma (T_{4}N_{0-2}M_{0-5}B_{0-1})</td>
<td>Erythroderma or Nodal (T_{4}N_{0-2}M_{0-5}B_{0-1})</td>
<td>Visceral (T_{4}N_{0-3}M_{1}B_{0-1})</td>
<td></td>
</tr>
</tbody>
</table>

- **Topical steroids (intermittent)**
- **Phototherapy (NB-UVB, PUVA)**
- **Bexarotene gel**
- **Tazarotene gel/cream**
- **Investigational agents (skin-directed)**

- **Phototherapy +/- IFN-α and/or +/- bexarotene**
- **ECP +/- IFN-α and/or +/- bexarotene, romidepsin, alemtuzumab**
- **Spot radiation, TSEBT**
- **Methotrexate, bexarotene, IFN-α**
- **HDACi (romidepsin, vorinostat)**
- **Investigational trials (e.g. brentuximab vedotin, anti-CCR-4)**
- **Single or multi agent chemotherapy (gemcitabine, pegylated doxorubicin, CHOP/CHOP-like regimens)**
- **Allogeneic transplant**
Care and Quality of Life

- Monitor for cutaneous infections
  - Bacterial (S. aureus)
  - Viral (HSV, VZV, HHV6)
- Monitor for other skin cancers
- Pruritus, pain
- Nutritional deficiencies
- Psychological needs
Disabling Pruritus and Pain

<table>
<thead>
<tr>
<th>Days</th>
<th>1 week</th>
<th>2 weeks</th>
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</thead>
<tbody>
<tr>
<td>06/11/16</td>
<td>Itching</td>
<td>Pain (skin)</td>
</tr>
<tr>
<td>06/14/16</td>
<td>Headache,</td>
<td>Rash, color of skin</td>
</tr>
<tr>
<td>06/17/16</td>
<td>Other symptoms:</td>
<td>Other symptoms:</td>
</tr>
<tr>
<td>06/20/16</td>
<td>Nausea, vomiting</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>06/23/16</td>
<td>Benadryl</td>
<td>Allegra</td>
</tr>
<tr>
<td>06/26/16</td>
<td>Kloroxepam</td>
<td>Emend</td>
</tr>
<tr>
<td>06/29/16</td>
<td>Nocodema</td>
<td>Prednisone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/12/16</td>
<td>Bad day</td>
</tr>
<tr>
<td>06/13/16</td>
<td>Itching</td>
</tr>
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</table>

<table>
<thead>
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<th>Days</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/16</td>
<td>Prednisone dosage</td>
</tr>
<tr>
<td>07/02/16</td>
<td>Prednisone dosage</td>
</tr>
<tr>
<td>07/03/16</td>
<td>Prednisone dosage</td>
</tr>
</tbody>
</table>

City of Hope
CD 30 + Lymphoproliferative Disorders
Lymphomatoid Papulosis

- Recurrent papulonodular lesions
  - Frequent ulceration
  - Spontaneous involution
- Indolent course
  - 10-20% associated with malignancy
- Fascin and CD134 predict progression
- TRAF1 expression distinguishes from ALCL
Cutaneous Anaplastic Large Cell Lymphoma

- Solitary or localized (ulcerating) nodules or tumors
- CD4⁺ CD30⁺ helper T-cell phenotype
- Overlap with LyP, transformed mycosis fungoides and cutaneous Hodgkin’s disease
- Anaplastic morphology, non-epidermotropic, large lymphocytes
- No t(2;5) translocation; ALK negative
Treatment Regimens

**LyP:**
- Observation
- **PUVA**
- **Low dose weekly oral methotrexate**
- NB-UVB and low dose oral Targretin (150 mg daily)
- topical steroid, topical bexarotene
- I.V. Brentuximab

**ALCL:**
- Radiation (solitary/localized)
- Weekly oral methotrexate
- Pegylated doxorubicin
- I.V. Brentuximab
25% - 30% of all cutaneous lymphomas are B-cell derived:

<table>
<thead>
<tr>
<th>WHO-EORTC Classification</th>
<th>Cutaneous B-cell Lymphomas</th>
<th>Frequency (%)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indolent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous marginal zone lymphoma</td>
<td>7</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous follicular lymphoma</td>
<td>11</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td><strong>Aggressive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell lymphoma, leg type</td>
<td>4</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell lymphoma, other</td>
<td>&lt;1</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

*WHO-EORTC (1905 patients), Blood 2005*
Primary Cutaneous Follicle Center Lymphoma

- Most common type of cutaneous B cell lymphoma
- Solitary plaques/tumors on trunk, head or scalp; rarely grouped lesions
- **CD20^+, Bcl-6^+, CD10^+, Bcl-2^−, MUM-1^-** (germinal center origin)
- Follicular, diffuse or mixed dermal infiltrate
  - Neoplastic follicle center cells
  - > Centrocytes (small to large cleaved cells) in low-grade PFCL
  - > Centroblasts (large round cells with prominent nuclei) in high-grade PFCL
- No t(14:18)
- Cutaneous relapses ~50%, extracutaneous dissemination 5-10%
Primary Cutaneous Marginal Zone Lymphoma (Immunocytoma)

- MALT-type lymphoma
- Solitary or multiple red-violaceous papules, plaques, nodules on trunk and arms
- Association with B. afzelii (Europe), but not USA
- Frequent relapses, rarely extracutaneous dissemination
- \( \text{CD20}^+, \text{CD79a}^+, \text{CD5}^-, \text{CD10}^-, \text{Bcl}-6^-, \text{Bcl}-2^+ \), phenotype
- \( \text{MUM}-1^+ \) (plasma cells)
- Transformation to diffuse large B-cell lymphoma possible
- Relapse rate 40-45%
Marginal Zone Lymphoma
Clinicopathologic Features
Primary cutaneous Diffuse Large B-cell Lymphoma, Leg Type

- Elderly females
- Solitary or multiple red-violaceous tumors mostly on lower legs, rarely at other sites
- CD20+, CD5-, CD79a+
- Bcl-2+/−, Bcl-6+/−, CD10−, MUM-1+, FOXP1+/−
- Frequent cutaneous relapses and extracutaneous dissemination
- No t(14:18)
- Chromosomal gains on chromosome 7p and 18q, loss of 6q
- Sheets of centroblasts and immunoblasts
- 5-year survival (multiple lesions): 50%
Primary Cutaneous DLBCL - Leg Type
Reclassification of 300 Primary Cutaneous B-Cell Lymphomas According to the New WHO–EORTC Classification for Cutaneous Lymphomas: Comparison With Previous Classifications and Identification of Prognostic Markers

Nancy J. Senff, Juliette J. Hoefnagel, Patty M. Jansen, Maarten H. Vermeer, Joop van Baarlen, Willeke A. Bloks, Marijke R. Canninga-van Dijk, Marie-Louise Geerts, Konnie M. Hebeda, Philip M. Kluit, King H. Lam, Chris J.L.M. Meijer, and Rein Willemze

5-y DSS:
- 71 pcMZL 98%
- 171 pcFCL 95%
- 58 DLBCL-LT 50%

Multivariate analysis for pcFCL:
FoxP1 expression and localization on leg carries poor prognosis
<table>
<thead>
<tr>
<th>PCBCL subtype</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent entities</td>
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<td></td>
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<tr>
<td>• PCFCL and PCMZL</td>
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<tr>
<td>o Solitary and/or localized skin lesions</td>
<td>• Observation</td>
<td>• No published data</td>
</tr>
<tr>
<td></td>
<td>• Intraleision steroids</td>
<td>• ORR 100%, CRR 44%</td>
</tr>
<tr>
<td></td>
<td>• Local radiation</td>
<td>• CRR 100%</td>
</tr>
<tr>
<td></td>
<td>• Surgical excision</td>
<td>• CRR 100%</td>
</tr>
<tr>
<td></td>
<td>• Intraleision interferon-α</td>
<td>• CRR 71%, PRR 23%</td>
</tr>
<tr>
<td></td>
<td>• Intraleision rituximab</td>
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<tr>
<td>o Disseminated skin lesions</td>
<td>• Observation</td>
<td>• No published data</td>
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<tr>
<td></td>
<td>• IV rituximab</td>
<td>• ORR 87%, CRR 60%</td>
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<tr>
<td></td>
<td>• Chemoimmunotherapy (R-Bendamustine)</td>
<td>• CRR 85%</td>
</tr>
<tr>
<td>o Cases associated with Lyme disease</td>
<td>• Systemic antibiotics (doxycycline, cefotaxime)</td>
<td>• Based on EORTC guidelines, isolated cases with CR</td>
</tr>
<tr>
<td>Aggressive entities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PCDLBCL-LT</td>
<td>• Chemoimmunotherapy (R-CHOP)</td>
<td>• CRR 92%</td>
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<tr>
<td></td>
<td>• Chemoimmunotherapy + RT (localized disease)</td>
<td>• No published data</td>
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<tr>
<td></td>
<td>• Palliative RT (localized disease)</td>
<td>• No published data</td>
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<tr>
<td></td>
<td>• Autologous stem cell transplant (relapse/ refractory cases)</td>
<td>• Isolated cases with CR</td>
</tr>
<tr>
<td></td>
<td>• Lenalidomide</td>
<td>• ORR 20%</td>
</tr>
<tr>
<td></td>
<td>• Clinical trials: Aurora kinase inhibitors, ofatumumab, lumiliximab,</td>
<td>• No published data</td>
</tr>
<tr>
<td></td>
<td>dacetuzumab, Ibrutinib, pembrolizumab.</td>
<td></td>
</tr>
</tbody>
</table>
Thank You!

City of Hope
- Steven Rosen
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- Linda Lee
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