Outline and Objectives

• Background
• Cutaneous adverse events (CAEs) from immune checkpoint inhibitor therapy
  – Updates
  – Treatment pearls
  – Hair and nails
• CAEs as prognostic indicators

Significance

• Quality of Life
  – Pain
  – Pruritus
  – Emotional/social impact
  – Activities of daily living

• Cancer therapy
  – 76%, EGFR inhibitors
    • 70% patients [reduction], 30% [discontinuation]
  – 30-50%, immune checkpoint inhibitors
    • 20% [reduction or discontinuation]

Background

Cytotoxic chemotherapy
- Target rapidly replicating cells
- Emergence in early 1900s
- Increased systemic toxicities
- Hair: Anagen effluvium
- Skin: Toxic erythema
- Nails: Onycholysis, Beau’s lines, Pigmentation change

Targeted therapies
- Targeted inhibition of small molecules
  - Higher efficacy for cancer treatment
- Emergence in early 1990s
- Decreased systemic toxicities
- New hair, skin, nail toxicities

Immune checkpoint inhibitors


Immune checkpoint inhibitors

CTLA4 inhibitors

- Ipilimumab: Mar 2011, metastatic melanoma
- Tremelimumab: failed Phase III trials for melanoma, Phase I-III trials for various solid organ malignancies

Immune checkpoint inhibitors

**PD-1 Inhibitors**
- Ipilimumab - Mar 2011, metastatic melanoma
- Pembrolizumab - Sep 2014, metastatic melanoma

**PD-L1 Inhibitors**
- Atezolizumab - May 2016, urothelial carcinoma
- Avelumab - March 2017, Merkel cell carcinoma
- Durvalumab - May 2017, urothelial carcinoma

**PD-1 Inhibitors**
- Nivolumab - Dec 2014, metastatic melanoma
- Pembrolizumab - Sep 2014, metastatic melanoma

**PD-L1 Inhibitors**
- Atezolizumab - May 2016, urothelial carcinoma
- Avelumab - March 2017, Merkel cell carcinoma
- Durvalumab - May 2017, urothelial carcinoma

Combination therapy
- Clinical trials, metastatic melanoma
Legend

- EGFR inhibitors
  - Erlotinib, Gefitinib, Cetuximab, etc
- Multikinase inhibitors
  - Sorafenib, Sunitinib, Regorafenib
- MEK inhibitors
  - Trametinib, Cabimetinib, etc
- BRAF inhibitors
  - Vemurafenib, Dabrafenib
- HER2 inhibitors
  - Lapatinib, Trastuzumab, Pertuzumab
- mTOR inhibitors
  - Sirolimus, Everolimus, Temsirolimus
- VEGF inhibitors
  - Pazopanib
- RET inhibitors
  - Vandetanib
- Bcr-Abl TKIs (2nd & 3rd gen)
  - Dasatinib, Nilotinib, Ponatinib

irAEs in Immune checkpoint inhibitors
Combination therapy: 62% CAEs (increased efficacy and increased toxicity)


Question

Erythema multiforme or Stevens Johnsons Syndrome has been reported with:
A. Immune checkpoint inhibitors
B. BRAF inhibitors
C. EGFR inhibitors
D. All of the above

Severe drug rashes

- Erythema multiforme
- Stevens Johnsons Syndrome
- Toxic Epidermal Necrolysis
- EGFRi
- BRAFi
- Anti PD1
- Anti CTLA4

Question
Doxycycline can be preventative for:
A. Acneiform eruption
B. Paronychia
C. Phototoxicity
D. A&B
E. All of the above

Acneiform eruption
- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- HER2 inhibitors
- mTOR inhibitors
- VEGF inhibitors
- RET inhibitors

Treatment options:
- Doxycycline 100 mg BID
- Hydrocortisone 2.5%
- Bland emollient
- Clindamycin 1%
- Silvadene

Dose reduction/cessation

Acneiform eruption
- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- HER2 inhibitors
- mTOR inhibitors
- VEGF inhibitors
- RET inhibitors

- Intralesional triamcinolone
- Oral prednisone
- Topical or oral retinoid
- Topical dapsone
- Salicylic acid peels
- Ivermectin
Acneiform eruption

- Mechanism
  - EGFR expressed in undifferentiated basal keratinocytes
  - Blockade causes
    - Early differentiation (increased KRT1, STAT3, p27)
    - Decreased replication (downregulated Ki67, MAPK)
    - Thin stratum corneum, abnormally differentiated epidermis, dyskeratosis
    - Follicular rupture → Inflammation and Pustules

Acneiform eruption

- Quality of life is key component
- Eruption scoring scale
  - Morphology and number of lesions
  - Symptoms
  - Blepharitis and paronychia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Papules and/or pustules covering % BSA</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>&lt;10% BSA, may or may not be associated with symptoms of pruritus or tenderness</td>
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<tr>
<td>Grade 2</td>
<td>10–30% BSA, may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact, limiting instrumental ADL</td>
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<tr>
<td>Grade 3</td>
<td>&gt;30% BSA, may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated</td>
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<tr>
<td>Grade 4</td>
<td>Any % BSA, may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences</td>
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Common Terminology Criteria for Adverse Events 4.0


Question

Which can be aided by good foot care/podiatry?
A. Hand foot skin reaction
B. Keratoderma
C. Paronychia
D. All of the above
Hand foot skin reaction (HFSR)

**Hand foot SYNDROME/Acral erythema:**
- Doxorubicin, 5-fluorouracil, capecitabine
- Diffuse erythema and edema

**Hand foot SKIN REACTION:**
- Tender, erythematous focal plaques (weight-bearing or friction)
- Hyperkeratosis or bullae

Hand foot skin reaction (HFSR)

**Hand foot SYNDROME**

**Hand foot SKIN REACTION**

**Keratoderma BRAF inhibitor**

Hand foot skin reaction

- **Multikinase inhibitors**
- **VEGF inhibitors**
- **Treatment options:**
  - Preventative foot care (orthotics, shaving calluses/bunions)
  - Topical keratolytics (urea, lactic acid)
  - Clobetasol 0.05%
  - Dose reduction/cessation
Hand-foot skin reaction

- **Mechanism**
  - VEGFR-related
    - Worse with beclizumab
    - Pressure and trauma with poor repair
  - Fas/FasL mediated
    - Blocked with anti-FasL antibody
    - Same mediators as SJS/TEN

Paronychia

- **EGFR inhibitors**
- **MEK inhibitors**
- **mTOR inhibitors**

  - Treatment options:
    - Treat superinfections
      - Oral antibiotics
      - Topical mupirocin and azole
    - ½ water: ½ vinegar soaks
    - Betamethasone 0.05% lotion
    - Oral doxycycline
    - Nail avulsion
    - Phenol chemical matricectomy
    - Topical povidone-iodine
    - Dose reduction/cessation

Question

Onycholysis is the most common nail side effect of immune checkpoint inhibitor therapy
A. True
B. False
Onycholysis

- Taxanes
  - docetaxel and paclitaxel
- Tetracyclines and psoralen
  - Photo-induced
- PD1 inhibitors
- Complications:
  - Subungual abscesses

Onychomadesis

- Any cytotoxic chemotherapy
- EGFR inhibitors
- Pathogenesis: Proximal nail matrix
- Clinical presentation: Shedding of the nail or a sulcus that splits the nail plate
  - Begins at the proximal nail fold
  - Extreme degree of Beau's lines

Question

Which is NOT a potential hair side effect of targeted cancer therapy?
A. Darkening of hair
B. Curling of hair
C. Scarring alopecia
D. All of the above are possible
Hair repigmentation

- **PD-1/PDL-1 inhibitors**
  - Time to onset: 19.5 cycles
  - Non small cell lung cancer
  - Associated with tumor response

Hair texture change

- **BRAF inhibitors**
  - reversible

Scarring alopecia

- **Bcr-Abl TKIs (2nd and 3rd gen)**
  - Treatment options:
    - Pruritus: antihistamines
    - Topical/IL steroids
    - Dose reduction/cessation
Question

6. Name two drugs that can induce the tumor they are being used to treat.
A. MEK inhibitor and CTLA4 inhibitor
B. MEK inhibitor and PD1 inhibitor
C. BRAF inhibitor and CTLA4 inhibitor
D. BRAF inhibitor and PD1 inhibitor

Keratinocytic neoplasms

- Multikinase inhibitors
- BRAF inhibitors
- PD-1 inhibitors
- Hedgehog pathway inhibitors
- JAK inhibitors

- Treatment options:
  - Reactive:
    - Cryotherapy
    - Electrodessication and curettage
    - Excision/Mohs
  - Preventative:
    - Oral retinoid
    - MEK inhibitor
    - Photodynamic therapy
    - Topical 5-FU

BRAF inhibitors

- Squamous papillomas
  - Hypertrophic actinic keratoses, irritated seborrheic keratoses, verruca

- Cutaneous squamous cell carcinoma
  - Vemurafenib: 25%
  - Dabrafenib: 7%
  - Mechanism: activates mutated HRAS
    - 21.2% from BRAF inhibitor tumors versus 3.2% from control tumors

Melanocytic neoplasms

- BRAF inhibitors
  - New nevi
- PD1 inhibitors
- CTLA4 inhibitors
  - Regression of nevi/tumoral melanosis

Treatment options:
- Skin exams
Melanocytic neoplasms

• Eruptive lentigines
  — Higher Cyclin D1 expression
  — MAPK pathway upregulation
  — Higher degree of atypia

• New primary melanoma
  — 5/468 patients, Phase II/III
  — Wild-type BRAF, all < 0.5 mm
  — Mechanism: activates MAPK signaling pathway for wild-type BRAF

• < 10% of patients required dose interruption

Melanocytic neoplasms

• Regressing nevi
  — Time to onset: 2-4 months


Question

Which is not a typical BRAF inhibitor toxicity?
A. Sweet’s
B. EN-like panniculitis
C. Phototoxicity
D. Acneiform eruption
E. Dysplastic nevi
### Erythema Nodosum

- **Multikinase inhibitors**
- **BRAF inhibitors**
- **CTLA4 inhibitors**
- **mTOR inhibitors**

**Treatment options:**
- None if asymptomatic
- NSAIDs
- Oral prednisone (5 mg)

### Phototoxicity

- **EGFR inhibitors**
- **BRAF inhibitors**
- **RET inhibitors**

**Treatment options:**
- Photoprotection
  - UPF clothing
  - Benzotriazol (Tinosorb S)
  - Bisabolol (Firework M)
  - Tris-Biphenyl Triazine (Tinosorb A2B)
  - Octyl methoxycinnamate (Tinosorb DMC)
- Oral or topical steroids

### Pruritus

- **EGFR inhibitors**
- **Multikinase inhibitors**
- **MEK inhibitors**
- **BRAF inhibitors**
- **HER2 inhibitors**
- **CTLA4 inhibitors**
- **PD-1 inhibitors**
- **mTOR inhibitors**
- **Bcr-Abl TKIs (2nd and 3rd gen)**
- **RET inhibitors**

**Treatment options:**
- Determine etiology
  - Scabies
  - Drug reaction to beta blocker
  - Eczema
  - Lichen planus
  - Xerosis
  - Acneiform eruption
- Oral antihistamines
- Emollients
- Topical steroids
- Antidepressants/antipsychotics
- Phototherapy
- Dose reduction/cessation
Question
7. Drug-induced _______ is seen with immune checkpoint inhibitors.
   A. Spongiotic dermatitis
   B. Psoriasiform dermatitis
   C. Lichenoid dermatitis
   D. Granulomatous dermatitis
   E. All of the above

Spongiotic dermatitis
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- Treatment options:
- Flare regimen:
  - Triamcinolone 0.1% BID (body)
  - Hydrocortisone 2.5% BID x 5 days (face, genital area)
  - Oral or systemic steroids
  - RTC: 2 weeks
- Maintenance regimen:
  - Topical steroid BW
  - Bland emollient daily
- Systemic therapy:
  - Anti IL4?

Psoriasiform dermatitis
- PD-1 inhibitors
- Treatment options:
- Flare regimen:
  - Triamcinolone 0.1% BID (body)
  - Hydrocortisone 2.5% BID x 5 days (face, genital area)
  - RTC: 2 weeks
- Maintenance regimen:
  - Topical steroid BW
  - Bland emollient daily
- Systemic therapy:
  - Oral steroids
  - Acitretin
  - Methotrexate
  - Anti IL17
### Lichenoid dermatitis

- **PD-1 inhibitors**

- **Treatment options:**
  - Topical steroid
  - Oral steroid
  - *Systemic retinoid*
  - *Methotrexate*
  - *Anti IL 17*
  - **Drug cessation**

### Granulomatous dermatitis

- **BRAF inhibitors**
- **CTLA4 inhibitors**
- **PD-1 inhibitors**

- **Treatment options:**
  - Topical steroid
  - Oral steroid
  - **Drug cessation**

### Bullous pemphigoid

- **PD-1 inhibitors**

- **Treatment options:**
  - Topical/oral/IV steroids
  - *Anti CD20?*
  - *Anti IgE?*
  - **Drug cessation**

  - Long latency (3-16 weeks)
Question

Using oral steroids will prevent the immune checkpoint inhibitor from working
A. True
B. False

Immunosuppression and Checkpoint inhibitors

- Systemic steroids and TNF inhibitors do not affect outcomes

Vitiligo

- CTLA4 inhibitors
- PD-1 inhibitors

- Treatment options:
  - Nothing
  - Topical steroids or topical tacrolimus +/- light therapy
Rashes as prognostic indicators

Who will get toxicities?
Who will respond to toxicity management?

Do toxicities predict tumor response?

Question

Prolonged response to immune checkpoint inhibitor therapy has been associated with?
A. Lung metastases
B. High functional status
C. Low-grade Immune-related adverse events
D. High-grade immune-related adverse events

Rashes as prognostic indicators

What we know
• Acneiform eruption with EGFR inhibitors
  – Non-small cell lung cancer
• Vitiligo with immune checkpoint inhibitors
  – Metastatic melanoma

Potential correlations
• Acneiform eruption with MEK inhibitors
• Granulomatous dermatitis with BRAF or immune checkpoint inhibitors
• Psoriasiform dermatitis with anti PD-1 therapy
Acneiform eruption

- **EGFR inhibitors**
- **Cancer types:**
  - Colorectal cancer
  - Non-small cell lung cancer
  - Head and neck SCC
- **Rash characteristics:**
  - Early appearance
  - Grade 2+
- **Correlation to:**
  - Progression-free survival
  - Overall survival
  - Tumor response
- **Histo:**
  - Decreased p-EGFR expression correlated to OS (normal skin)

Vitiligo

- **Immune checkpoint inhibitors**
- **UNDER REPORTED**
  - Retrospective
  - Clinical trials run by oncologists
- **Cancer types:**
  - Melanoma
- **Correlation to:**
  - Progression-free survival
  - Tumor response


- **67 patients**
- **Prospective**
- **Incidence of vitiligo: 25%**
- **Time to onset:**
  - 52 to 453 days
  - median, 126 days
- **Tumor response:**
  - Higher occurrence of vitiligo
  - 71% vs. 28%
  - 3/17 (18%) had a complete response
  - 9/17 (53%) had a partial response
  - 3/17 (18%) had stable disease
  - 2/17 (12%) had progressive disease
Granulomatous reactions

- Indicate immune response
  - Hodgkin's disease
  - Gastric adenocarcinoma
- BRAF inhibitors
- Anti CTLA4
- Anti PD-L1

Granulomatous dermatitis

- BRAF inhibitors
  - 3 patients
  - Time to onset: 2-10 months
  - Erythematous, and violaceous papules
  - Tumor response (2), progression of disease (1)

Sarcoidosis

- Ipilimumab (11), Anti-PD-L1 (1)
- Cancer type:
  - Melanoma
  - Prostate CA
  - Lung adenCA
- Sarcoidosis presentation:
  - Lung, filling spleen, skin
  - Skin 2 in combination with lung, 1 primary
  - 6/8 Partial or complete remission
  - 1/8 Stable disease
  - 3/8 Progression of disease
Psoriasiform dermatitis

- Anti PD-1
  - PD-L1 expression is increased in melanoma tumor cells
  - PD-1 expression is increased in Th17 cells in psoriatic lesions

Summary

- Cutaneous toxicities from targeted cancer therapy are significant
- Old rashes in a new context
- CAEs can be a window into drug mechanisms and tumor response

Thank you

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References


