Melanoma Systemic Therapy: Side Effects and Management Strategies

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Outline and Objectives

• Background
• Cutaneous adverse events (CAEs) from novel melanoma therapy
  – Targeted therapy
  – Immunotherapy
  – T-cell mediated
  – Antibody-mediated
  – Neoplastic
• CAEs as prognostic indicators
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
Legend

- **BRAF inhibitors**
  - Vemurafenib- FDA approved, metastatic melanoma
  - Dabrafenib- FDA approved, metastatic melanoma
  - Encorafenib- FDA approved, metastatic melanoma

- **MEK inhibitors**
  - Trametinib- FDA approved, metastatic melanoma
  - Cobimetinib- FDA approved, metastatic melanoma
  - Binimetinib- FDA approved, metastatic melanoma
  - Selumetinib- Phase III trials, NSCLC
Immune checkpoint inhibitors

Immune checkpoint inhibitors

**Immune checkpoint inhibitors**

*CTLA4 inhibitors*
- Ipilimumab - Mar 2011, metastatic melanoma
- Tremelimumab - failed Phase III trials

*PD-1 inhibitors*
- Nivolumab - Dec 2014, metastatic melanoma
- Pembrolizumab - Sep 2014, metastatic melanoma
- Cemeplimab - cutaneous squamous cell carcinoma

*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
Significance

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

• **Cancer therapy**
  – 30-50%, immune checkpoint inhibitors
    • 20% (reduction or discontinuation)
  – Higher with combination therapy
  – Neoadjuvant, adjuvant,

Repurposed rashes
Acneiform eruption

- **MEK inhibitors**
- **CTLA4 inhibitors**

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

- **Dose reduction/cessation**
<table>
<thead>
<tr>
<th>Acneiform eruption</th>
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<tbody>
<tr>
<td><strong>MEK inhibitors</strong></td>
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<tr>
<td><strong>CTLA4 inhibitors</strong></td>
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<tr>
<td>Isotretinoin 40 mg daily</td>
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<tr>
<td>Acitretin 10 mg daily</td>
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<tr>
<td><strong>Intralesional triamcinolone</strong></td>
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<td><strong>Oral prednisone</strong></td>
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<td><strong>Topical or oral retinoid</strong></td>
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<td><strong>Topical dapsone</strong></td>
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<td><strong>Salicylic acid peels</strong></td>
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<td><strong>Ivermectin</strong></td>
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Acneiform eruption

- Folliculitis
  - Yeast or bacteria
- Steroid acne
  - Prolonged systemic steroid use
- Acneiform eruption
- Super-infected acneiform eruption
Acneiform eruption

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

Erythema nodosum

- BRAF inhibitors
- CTLA4 inhibitors
- Autoimmune disease
- Infection
- Idiopathic

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

- **BRAF inhibitors**
- **Treatment options:**
  - Photoprotection
    - UPF clothing
    - Bemotrizinol (Tinosorb S)
    - Bisoctrizole (Tinosorb M)
    - Tris-Biphenyl Triazine (Tinosorb A2B)
    - Octyl methoxycinnamate (Tinosorb OMC)

- Oral or topical steroids
Eczema

- **CTLA4 inhibitors**
- **PD-1 inhibitors**
- **PD-L1 inhibitors**
- **Atopic dermatitis**
  - Flexural, FMH/PMH
  - Dry skin
- **Allergic contact dermatitis**
  - Geometric, pt history

**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 BIW
- Bland emollient daily

**Systemic therapy:**
- Anti IL4?
Psoriasiform dermatitis

- **PD-1/PD-L1 inhibitors**
- **Psoriasis**
- **Oral steroids**
- **Oral retinoids**
- **Methotrexate**
- **Biologics** - TNF blockers - Anti IL23 - Anti IL17

- **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 BIW
  - Bland emollient daily
Lichenoid dermatitis

- *PD-1/PD-L1 inhibitors*
- Lichen planus
- Lichenoid drug eruption

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

- **BRAF inhibitors**
- **CTLA4 inhibitors**
- **PD-1/PD-L1 inhibitors**
- Primary granulomatous dermatitis
  - Cutaneous sarcoidosis
  - Granuloma annulare
- **Secondary granulomatous dermatitis**
  - Infection (atypical)
  - Foreign Body

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

- **CTLA4 inhibitors**
- **PD-1/PD-L1 inhibitors**

Treatment options:
- Nothing
- Topical steroids or topical tacrolimus +/- light therapy
Bullous pemphigoid

- **PD-1 inhibitors**
- **PD-L1 inhibitors**

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

- Long latency (3-16 weeks)
Systemic steroids and TNF inhibitors do not affect outcomes (that we know of)
Dermatomyositis

- **CTLA4 inhibitors**
- **PD-1 inhibitors**
- Paraneoplastic
- Autoimmune

- Treatment options:
  - Oral steroids
  - Methotrexate
  - Hydroxychloroquine
  - IVIG
  - Dose reduction/cessation
Xerosis

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

**Treatment options:**
- Bland emollient BID
- Bath BID
- Keratolytics (ammonium lactate or salicylic acid)
- Topical steroid PRN
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
Keratinocytic neoplasms

- **BRAF inhibitors**
- **PD-1/PD-L1 inhibitors**

Treatment options:
- Reactive:
  - Cryotherapy
  - Electrodermabrasion 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

PD1 inhibitors

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

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

Rashes as prognostic indicators

Who will get toxicities?

Do toxicities predict tumor response?

Who will respond to toxicity management?
Rashes as prognostic indicators

What we know

• Acneiform eruption with EGFR inhibitors
  – Non-small cell lung cancer
  – Colorectal 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
Conclusion

• Could this be a therapy-related CAE?
  – Is it T-cell mediated?
  – Is it antibody-mediated?
  – Is it neoplastic?

• Diagnosis and management
  – Business as usual

YES!!
References


References

References


