Cutaneous adverse events to immune checkpoint inhibitor therapy

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Outline and Objectives

• Background
• Cutaneous adverse events (CAEs) from immune checkpoint inhibitor therapy
• CAEs as prognostic indicators

Immune checkpoint inhibitors

Immune checkpoint inhibitors

Legend

- CTLA4 inhibitors
  - Ipilimumab: Mar 2011, metastatic melanoma
  - Tremelimumab: Phase III trials
- PD-1 Inhibitors
  - Nivolumab: Dec 2014, metastatic melanoma
  - Pembrolizumab: Sep 2014, metastatic melanoma
- PD-L1 Inhibitors
  - Atezolizumab: May 2016, urothelial carcinoma
  - Avelumab: Phase III trials
  - Durvalumab: Phase III trials

Immune checkpoint inhibitors

Spongiotic dermatitis

- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors

Spongiotic dermatitis
### 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 BIW
  - Bland emollient daily

### Psoriasiform dermatitis

- PD-1 inhibitors

### Psoriasiform dermatitis

- Image of histological sections of skin tissue, showing typical features of psoriasiform dermatitis.
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
    - Systemic retinoids
    - Anti IL 17
  - Maintenance regimen:
    - Topical steroid BIW
    - Bland emollient daily

Granulomatous dermatitis

- **BRAF inhibitors**
- **CTLA4 inhibitors**
- **PD-1 inhibitors**
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Lichenoid dermatitis
Lichenoid dermatitis

- PD-1 inhibitors
- Treatment options:
  - Topical steroid
  - Oral steroid
  - Systemic retinoid?
  - Methotrexate?
  - Anti IL 17?
  - Drug cessation

Bullous pemphigoid

- PD-1 inhibitors
### Bullous pemphigoid

- **PD-1 inhibitors**
- **Treatment options:**
  - Topical/oral/IV steroids
  - Drug cessation
  - Long latency (3-16 weeks)

### Vitiligo

- **CTLA4 inhibitors**
- **PD-1 inhibitors**
- **Treatment options:**
  - Nothing
  - Topical steroids or topical tacrolimus +/- light therapy
  - Possible association with PFS and tumor response
Rashes as prognostic indicators

- 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

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)

MEK inhibitors? RET inhibitors?
Vitiligo

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

**5,737 patients**

- Incidence of vitiligo: 3.4%
- Progression free survival: HR 0.51
- Overall survival: HR 0.25

**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
• 148 patients
  • Incidence of rash: 54.6%
• Incidence of vitiligo:
  • Time to onset:
  • Had been previously treated with IL-2
  • Reported iAEs:
  • Improved OS:

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 [12], Anti-PD-L1 [1]
- **Cancer types:**
  - Melanoma
  - Prostate CA
  - Lung adeCA

- **Sarcoidosis presentation:**
  - Lung, kidney, spleen, skin
  - Skin: 2 in combination with lung, 1 primary
  - 4/8: Partial or complete response
  - 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

- CAEs can be a window into drug mechanisms and tumor response
- Things we know:
  - Acneiform eruption indicates a good prognosis for some cancers
  - Vittiligo indicates a good prognosis for melanoma
- Potential correlations:
  - Granulomatous reactions
  - Psoriasiform dermatitis

Thank you

- Shelby Kubicki, MS2
- Macartney Welborn, MS2
- Osama Hashmi, MS4
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- Saira George, MD

References