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
Legend

• **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

• **PD-L1 inhibitors**
  • Atezolizumab- May 2016, urothelial carcinoma
  • Avelumab- Phase III trials
  • Durvalumab- Phase III trials
Most common inflammatory CAE from ipilimumab?

A. eczema
B. psoriasis
C. mucositis
D. acneiform
E. vitiligo
Most common inflammatory CAE from ipilimumab?

A. **eczema**
B. psoriasis
C. mucositis
D. acneiform
E. vitiligo
Question 8

What is the sentinel irAE from ipilimumab?

A. Rash
B. Colitis
C. Pneumonitis
D. Myocarditis
E. Thyroiditis
Eczema

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET 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

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET 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
  - Maintenance regimen:
    - Topical steroid BIW
    - Bland emollient daily
Granulomatous dermatitis

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors

- Treatment options:
  - Topical steroid
  - Oral steroid
Xerosis

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors

Treatment options:
- Bland emollient BID
- Bath BID
- Keratolytics (ammonium lactate or salicylic acid)
- Topical steroid PRN
Bullous pemphigoid

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors

- Treatment options:
  - Topical/oral/IV steroids
  - Drug cessation
  - Long latency (3-16 weeks)
Definitive treatment for anti-PD1-induced bullous pemphigoid is:

A. Dose reduction
B. Dose cessation
C. Systemic steroids
D. Systemic non-steroidal immunosuppression
Vitiligo

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors

**Treatment options:**
- Nothing
- Topical steroids or topical tacrolimus +/- light therapy
- Possible association with PFS and tumor response
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
Rashes as prognostic indicators
Question 10

CAE associated with tumor response?

A. Acneiform
B. Vitiligo
C. Hand foot skin reaction (HFSR)
D. A and B
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:
  – 46 (40%) unresectable
  – 18 (54.6%) resected
  – 43% total

• Incidence of vitiligo:
  – 11 (9.6%) unresectable
  – 8 (24.2%) resected
  – 13% total

• Time to onset:
  – 5 weeks

• 3 had been previously treated with IL-2

• Reported irAEs:
  – Rash
  – Vitiligo
  – Endocrinopathies
  – Colitis
  – Pneumonitis

• Improved OS:
  – Rash: HR, 0.423
  – Vitiligo: HR, 0.184

- 83 patients
- Retrospective

Cancer types:
- Metastatic melanoma
- Lung cancer
- Prostate cancer
- Merkel cell CA

CAEs:
- 42% total incidence
- Macular papular eruption: 29%
- Pruritus: 12%
- Hypopigmentation: 8% (MELANOMA ONLY)
- Correlated with longer progression-free intervals
- HR 0.12 – 0.82 depending on dose
Question 11

Vitiligo as a CAE has only been reported in melanoma patients:

A. True
B. False
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)

• Ipilimumab (11), Anti-PD-L1 (1)

• **Cancer type:**
  – Melanoma
  – Prostate CA
  – Lung adenoCA

• **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

Question 12

Potential CAEs associated with tumor response?

A. Eczema
B. Psoriasis
C. Granulomatous dermatitis
D. All of the above
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

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

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

References


