U065- Update on Cutaneous Reactions to Targeted and Immune Therapy

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Outline and Objectives

- Last year: Hair, Nail, Neoplastic AEs
- What’s new?
  - Combination therapies
  - Derm-Rheum disease
  - Mucosal disease
  - Skin of color
Outline and Objectives

• Background
• Managing Patient Expectations
• Combination Therapies
• Derm-Rheum Adverse Events
• Mucosal Adverse Events
• Skin of Color
• MOC Questions
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Significance

• **Quality of Life**
  – Symptoms: pain, pruritus
  – Emotional/social impact
  – Activities of daily living

• **Managing expectations**

• **Multidisciplinary approach**

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

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, mucosal toxicities
Cellular targets to cancer therapy

- EGFR
- Mabs
- Cetuximab
- Erlotinib

- Nibs
- Sorafenib
- Vemurafenib

- RTK
- RAS
- PI3K/AKT

- RAF
- MEK
- MAPK/ERK

- Tumorigenesis

Legend

- **EGFR inhibitors**: Erlotinib, Gefitinib, Cetuximab, Pantitumumab
- **Multikinase inhibitors**: Sorafenib, Sunitinib, Regorafenib, Pazopanib
- **MEK inhibitors**: Trametinib, Cobimetinib, Binimetinib
- **BRAF inhibitors**: Vemurafenib, Dabrafenib, Encorafenib
- **HER2 inhibitors**: Lapatinib, Trastuzumab, Pertuzumab
- **mTOR inhibitors**: Sirolimus, Everolimus, Temsirolimus, Ridaforolimus
- **VEGF inhibitors**: Pazopanib, Regorafenib, Lenvatinib, Motesanib, Pegaptinib
- **RET inhibitors**: Vandetanib, Cabozantinib
- **Bcr-Abl TKIs**: Imatinib, Dasatanib, Nilotinib, Ponatinib, Bosutinib
- **JAK inhibitors**: Ruxolitinib, Tofacitinib, Oclacitinib, Baricitinib
Question

Immune checkpoint inhibitors upregulate the host tumor response.

A. True
B. False
Immune checkpoint inhibitors

CTLA-4 Pathway Inhibition

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

**PD-1 inhibitors**
- Nivolumab- Dec 2014, metastatic melanoma
- Pembrolizumab- Sep 2014, metastatic melanoma
- Cemiplimab- Sep 2018, 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
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Managing patient expectations

- I know you don’t feel this way, but this actually ISN’T THAT BAD
- NOT an allergic reaction *(usually)*
- This DOES NOT mean you have to stop your cancer therapy *(usually)*
- WILL NOT completely resolve
- WE KNEW this could happen
- We want you to be COMFORTABLE
- We want you to get the BEST cancer therapy for you
- We want to treat your skin with the LOWEST potential side effects
- Managing ONCOLOGIST expectations
  - We can keep this under control so that you can do your job
  - We will follow up closely with the patient so that you don’t have to worry about their skin
  - Can I use PO steroids? Can I use retinoids? Can I use other immunosuppressants (MTX, anti IL17, anti IgE, anti IL4, anti CD20)?
- 2 week follow up

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Combination Therapies

*The wave of the future!*

- **Melanoma (and others):**
  - Immune checkpoint inhibitor x 2

- **Colorectal cancer:**
  - Immune checkpoint inhibitors + (EGFR or MEK or multikinase inhibitor)
Combination Therapies

The wave of the future!

• Melanoma (and others):
  – Immune checkpoint inhibitor x 2

• Colorectal cancer:
  – Immune checkpoint inhibitors + (EGFR or MEK or multikinase inhibitor)
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 BIW
  - 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 BIW
    – 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
Question

Using oral steroids will prevent the immune checkpoint inhibitor from working

A. True
B. False
Immunosuppression

- Systemic steroids and TNF inhibitors do not affect outcomes
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

Bullous pemphigoid

- PD-1 inhibitors
- Treatment options:
  - Topical/oral/IV steroids
  - Anti CD20?
  - Anti IgE?
  - Drug cessation
- Long latency (3-16 weeks)
Combination Therapies

*The wave of the future!*

- Melanoma (and others):
  - Immune checkpoint inhibitor x 2

- Colorectal cancer:
  - Immune checkpoint inhibitors + (EGFR or MEK or multikinase inhibitor)
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
- Combination with immune checkpoint inhibitors
Acneiform eruption

- Intraluminal triamcinolone
- Oral prednisone
- Topical retinoid
- Topical dapsone
- Salicylic acid peels
- Ivermectin

- Drug holidays (3-5 days)
- Acitretin 10 mg daily
- Isotretinoin 40 mg daily
  - Easier insurance approval
  - No waiting period
Acneiform eruption

• I did everything you said, but...
  – Patient is still uncomfortable!
  – Patient was doing well, but recently flared!
Phototoxicity

- EGFR inhibitors
- BRAF inhibitors
- RET 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
Acneiform eruption

• I did everything you said, but...
  – Patient is still uncomfortable!
  – Patient was doing well, but recently flared!

• UV exposure
• Superinfection
• Call your oncologist
  – Drug holidays
  – Intermittent PO steroids
  – Reduce dose of offending drug
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

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
- Topical povidone-iodine
- Phenol chemical matricectomy
- Dose reduction/cessation
Question

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

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

**More commonly:**
- Large vessel vasculitis
- CNS and PNS vasculitis
- Longer time to onset: median 3 months

**Less commonly:**
- Granulomatous polyangiitis
- Possibly shorter time to onset
- No systemic involvement with LCV reports

**Treatment options:**
- Hydroxychloroquine
- Systemic steroids
- Dose discontinuation
Dermatomyositis

- CTLA4 inhibitors
- PD-1 inhibitors
- PD-L1 inhibitors

Treatment options:
- Oral steroids
- Methotrexate
- Hydroxychloroquine
- Dose reduction/cessation
Derm-Rheum Adverse Events

- Lupus erythematosus
- Sjogren’s disease
- Dermatomyositis
- Vasculitis
- Paraneoplastic
- Unmasking
- Drug-induced
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Stomatitis

- mTOR inhibitors
- Multikinase inhibitors
- EGFR inhibitors
- HER2 inhibitors
- VEGFR inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- PD-L1 inhibitors

- Treatment options:
  - Good oral hygiene
  - Topical steroids
  - Oral steroids
  - Avoid alcohol-based mouthwashes or chlorhexidine

- Low grade, self resolves
Other mucosal disease

- Migratory glossitis - mTORi
- Osteonecrosis of the jaw - VEGFRi
- Oral lichen planus Bcr- Abl TKIs, anti PD-1
- Dysgeusia - PTCHi
- Hyperkeratotic mucosal lesions - BRAFi
- Xerostomia - all
- Sjogren’s- like xerostomia - anti CTLA-4, anti PD-1, anti PD-L1

**Treatment options:**
- Good oral hygiene
- Topical steroids
- Oral steroids
- Avoid alcohol-based mouthwashes or chlorhexidine
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Drug-induced vitiligo only occurs in melanoma patients:

A. True
B. False
Vitiligo

- CTLA4 inhibitors
- PD-1 inhibitors

Treatment options:
- Nothing
- Topical steroids or topical tacrolimus +/- light therapy
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Exacerbating factors for acneiform eruptions include:

A. Phototoxicity
B. Superinfection
C. Use of alcohol-based products
D. Eating too much chocolate
E. A, B, and C
Question

Mucosal adverse events to targeted or immune checkpoint therapies are:

A. Low grade
B. Can be managed with good oral hygiene
C. Often self resolve
D. Can be managed with oral or topical steroids
E. All of the above
The most common type of checkpoint inhibitor induced vasculitis is:

A. Large vessel
B. Medium vessel
C. Small vessel
D. ANCA-positive
Combination therapies include:
A. Cytotoxic and targeted combos
B. Multiple checkpoint inhibitor combos
C. Multiple targeted inhibitor combos
D. All of the above
Combination therapies have increased dose-limiting toxicities compared to monotherapies.

A. True
B. False
Take home points

• Cutaneous toxicities have a high prevalence in targeted and immune therapies
• Managing patient expectations and working with the oncologist are critical for best compliance and quality of life
• Combination therapy has more toxicities than monotherapy
• Cutaneous vasculitis is rare
• Stomatitis (not mucositis) is low-grade and can be self limited
• Consider the needs of your patients with skin of color
Thank you

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

References

References


