Oral mucositis associated with targeted therapy and immunotherapy: what's old is new again

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# Faculty Disclosure

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Outline

- **Targeted therapies**
  - mTOR inhibitors
  - MEK inhibitors
  - PI3K inhibitors
  - anti-VEGF TKIs
  - EGFR inhibitors
  - BRAF inhibitors

- **Immune checkpoint inhibitors**
  - CTLA4 inhibitors
  - PD-1/PDL-1 inhibitors

mTOR inhibitor-associated stomatitis

• mTOR pathway
  – PI3K/AKT/mTOR frequently upregulated, proliferation
  – sirolimus, temsirolimus, everolimus

• Clinical features
  – aphthous-like ulcers
  – acute onset, days to weeks
  – recurrent, diminish with time
  – dose dependent

• Management
  – topical steroids
  – palliative care
  – dose modification

mIAS management w/ corticosteroids

- Retrospective, open label phase 1/2 trials
  - 17 cancer patients, everolimus/ridaforolimus
  - 10 days median onset (4–25)
    - median pain = 7/10
    - 5 dose reductions, 1 DLT
  - improvement in ~90% w/ steroid therapy
    - topical (15), intralesional (5), systemic (1)
    - palliative treatments w/ limited benefit

- SWISH trial (n = 92), open label phase 2
  - advanced HR+/HER2+ breast ca
  - EVE 10 mg/EXE 25 mg
  - dexamethasone 0.5 mg/5 mL, 2 min, s/s, QID
  - incidence of ≥ grade 2 stomatitis at 8 wks compared w/ BOLERO-2:
    - 2.4% vs. 33% (p <0.001), 21.2% vs. 67% all grades

Aphthous stomatitis w/ other targeted therapies?

- **PI3K inhibitors**
  - idelalisib
    - multiple phase 1 and 2 studies, no mucositis
  - copanlisib
    - phase 1, 6/57 (11%) w/ “oral cavity mucositis”, table, no description
  

- **MEK inhibitors**
  - trametinib (selumetinib, cobimetinib)
  - “mucositis”/“mucosal inflammation” reported infrequently (2-36%), aphthous-like? no description...
  
  
  - acneform rash common
  

MEK inhibitors
idelalisib (PI3K inhibitor)

MEK+ PI3K inhibitor
Oral dysesthesia associated w/ TKIs

• Multi-targeted tyrosine kinase inhibitors
  – anti-VEGF
  – sunitinib, sorafenib, others

• Clinical features
  – poorly described in literature
  – normal appearing mucosa
  – oral/tongue sensitivity, dysesthesia, taste changes
  – association w/ hand-and-foot skin reaction, increasing severity

• Management?
  – treat as pain or dysesthesia?
  – diet modifications

Sunitinib oral toxicity

• Mucosal sensitivity
  – most ≤ grade 2
  – <10% required dose reduction
    • <1% required discontinuation

• Clinical course
  – 7-14 days after start/severity increases
  – resolves during 2 wk rest
  – recurs, severity lessens

• Clinical findings normal
  – single report of “bullous mucositis” (?)

Immunotherapy-associated oral AEs

- **Immune checkpoint inhibitors**
  - block CTLA-4, PD-1/PD-L1; T cell activation
  - ipilimumab, nivolumab, pembrolizumab

- **Clinical features**
  - lichenoid inflammation, (bullous pemphigoid)
    - ~3 months mean onset (cutaneous); highly variable, case reports/series, multisystem possible
  - sicca syndrome (n=4, Hopkins, abrupt onset of severe hypofunction, timeframe variable)
  - GVHD after alloHSCT (relapse), potentially severe/refractory
    - acute, overlap, chronic forms
  - combination therapy w/ higher rates

- **Management**
  - lichenoid – topical steroids, +/- modifications
  - sicca – palliative, sialogogues, dental
  - early recognition, referral

nivolumab x 2 neoadjuvant head and neck cancer protocol
nivolumab-associated lichenoid inflammation, managed with topical clobetasol 0.05% solution
acute GVHD eruption following 1st cycle of pembrolizumab for metastatic colon cancer, s/p RIC alloHSCT for AML
Other reported oral toxicities

• Imatinib
  – lichenoid reactions, cheilitis, SJS
• EGF inhibitors
  – mucositis, ‘which rarely includes aphthous ulcers’, ‘without mucosal changes’
• Vemurafenib
  – mucosal keratosis
    • symptomatic, gingiva, palate, linea alba, labial
    • regressed on discontinuation
  – SCC (lower lip, n = 1)
• Benign migratory glossitis/erythema migrans
  – bevacizumab, sunitinib, sorafenib (anti-VEGF?...)

References:
s/p alloHSCT, cGVHD, s/p IL-2, mild symptoms

s/p alloHSCT, cGVHD, de novo, severe symptoms
Summary

• Novel cancer therapies, novel oral toxicities, but mimic other conditions
• Understand risk, recognize early signs/symptoms
• Patient education, prevention, awareness
• Management depends on correct diagnosis, specialty referral
• Research opportunities abound