Conflict of Interest Disclosure
Joanne Bowen, PhD

- Contracted Research
  - Puma Biotechnology
  - Pfizer Pharmaceuticals
  - AstraZeneca
  - Helsinn Healthcare
  - Entera Health Inc.
Goals of this talk

• Compare and contrast oral v GI mucositis
  – Common, overlapping, and unique features

• Highlight new insights from review
  – Emerging targets and technologies
Alimentary Tract

(pathobiology)
# Mucositis – a continuing problem

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicycle chemotherapy (solid tumors)</td>
<td>5-40% oral mucositis</td>
</tr>
<tr>
<td></td>
<td>Up to 50% diarrhea</td>
</tr>
<tr>
<td>Conditioning chemotherapy for HSCT</td>
<td>~85% oral mucositis (+TBI)</td>
</tr>
<tr>
<td></td>
<td>~40% oral mucositis</td>
</tr>
<tr>
<td></td>
<td>~50% diarrhea</td>
</tr>
<tr>
<td>Radiotherapy for HNC</td>
<td>60-90% oral mucositis</td>
</tr>
<tr>
<td></td>
<td>15-29% diarrhea</td>
</tr>
</tbody>
</table>

Sonis et al, PharmacoEconomics (2013) 31:753–766
Overlap of pathobiology/symptoms

- Example of local therapy causing GI disturbance

Challenges for OM and GIM research

• Differences in timing dependent on:
  – radiation vs chemotherapy (weeks vs days); regional location (GI ~5 days, Oral ~9 days)
  – Rodents resistance to ulceration
Key signalling processes

ROS
DAMP release
Clonogenic death
PRR activation

NFκB
TNF, IL-1b

Cell injury & death
Innate cell entry
TNF, IL-1b, IL-6

Ulcer
PAMPs, Innate cells
Cytokine feedback

ECM signals
Proliferations
Migration

Reactive oxygen species (ROS)
Pro-inflammatory cytokines, proteins
Anti-inflammatory cytokines
Nuclear factor kappa B (NFκB)
Tumor necrosis factor (TNF)
Interleukin (IL)-6, IL-1
Ceramide synthase

Ulcer
PAMPs, Innate cells
Cytokine feedback

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Pathogenesis review

- Brings both OM and GIM studies (preclinical and translational) together to identify new areas of research, biomarkers, mechanistic targets, experimental interventions.
Pathogenesis review findings
Pathogenesis key areas

• Established and emerging mediators of toxicity
  – Microbiome and host immune response
  – Sophisticated targeting of inflammation
  – Altered functional physiology

• Technological advances

• Perspective
Mediators of toxicity - microbiome

• Shifts in oral microbial composition during development OM has been long recognized and targeted

• Role for gastrointestinal (GI) flora in intestinal injury has only more recently been appreciated but accelerating

• To be determined is whether baseline composition OR change during therapy is most critical to mucositis development
Mediators of toxicity – oral microbe studies

• Patient studies have looked at overall diversity of oral flora and shifts during chemotherapy to determine relationships with oral mucositis risk and severity

• In vitro models of oral keratinocytes have demonstrated how microbes:
  – impact healing (30% decrease in wound closure)
  – change themselves during exposure to irradiation and 5-FU (sensitivity and virulence)
Mediators of toxicity – gut microbe studies

Montassier et al 2015, AP&T 42: 515-28
Technologies

• **Move from reductionist to systems biology approach**
  – Capitalizing on genomics, proteomics, metabolomics, microbiomics

• **Multi-cellular models (progress but limited complexity)**
  – 3D organoids with microinjection of microbes
  – Gut-on-a-chip with mucus and fluid sheer
  – Mesenchymal stem cells (radiation-induced chronic inflammation models)

• **Germ-free (GF) mice**
GF mice - OM vs GIM

- GF mice are resistant to 5-FU-induced oral mucositis

GF mice - OM vs GIM

- GF mice are protected from irinotecan GIM
- Conv FMT restores conventional phenotype

Antibiotics: Chemotherapy-induced

Antibiotics: Radiation-induced OM

OM score

Days

OM Score (Mean)

AbxRx

Rx

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Future Research
1. Defining role of oral v colonic microbiome
2. Comparative signatures across species
3. Know which to selectively modify and when
Take home messages

• Microbiome is a new frontier for whole body inflammatory signaling and effort is needed to characterize changes in different tract compartments

• Outcome measures in animal models must reflect changes in clinical settings and whole tract changes where possible

• Increased complexity of mucositis pathogenesis related to combination regimens - research must get on the leading edge
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Cancer Treatment Toxicities Group