SCIENTIFIC SESSION: MUCOSITIS

ALIMENTARY MUCOSITIS: PUTTING THE GUIDELINES INTO PRACTICE

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INTRODUCTION

• Objectives

1. To illustrate the problem of Alimentary Mucositis

2. To demonstrate practical use of the MASCC/ISOO mucositis guidelines

3. To discuss strategies for improving mucositis management
WHAT IS ALIMENTARY MUCOSITIS?

• Mucositis of the entire alimentary canal:

• Oral Mucositis plus Gastrointestinal Mucositis
LESSONS LEARNED FROM ORAL MUCOSITIS

- Extend to the entire GI tract
THE ALIMENTARY CANAL

- The GI tract is all one tube from mouth to anus—formed from primitive endoderm
Perspectives on Cancer Therapy-Induced Mucosal Injury

**Pathogenesis, Measurement, Epidemiology, and Consequences for Patients**

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**BACKGROUND:** Increasing complication of enteral treatment, oral and gut irradiation (OGI) mucositis, the effectiveness of therapy begins to lead to fewer complications. Endoscopic, radiographic, and histopathologic findings support this hypothesis. The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology assembled an international multidisciplinary panel of experts to create clinical practice guidelines for the prevention, evaluation, and treatment of mucositis.

**METHOD:** The panel members reviewed the literature published from January 1994 through May 2004, presented their findings, and reviewed a summary of the literature that produced two articles: the current study and another that examines the clinical implications of the panel's findings to practice guidelines.

**RESULTS:** New evidence supports the view that oral mucositis is a complex process involving all the tissue and cellular elements of the mucosa. Other findings suggest that some aspects of mucositis may be determined genetically. GI perspectives and clinical practice guidelines for the prevention and treatment of Cancer Therapy–Induced Oral and Gastrointestinal Mucositis

**Clinical Practice Guidelines for the Prevention and Treatment of Cancer Therapy–Induced Oral and Gastrointestinal Mucositis**

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**BACKGROUND:** Oral and gastrointestinal (GI) mucositis can affect up to 90% of patients undergoing high-dose chemotherapy and hematopoietic stem cell transplantation. GI mucositis can be a cause of mortality and morbidity, and contributes to other healthcare costs. Consequently, the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology assembled an expert panel to examine the literature and to create evidence-based guidelines for the prevention, evaluation, and treating mucositis.

**METHODS:** Thirty-six panelists reviewed extensive literature published from January 1994 to May 2004. An initial meeting in January 2004 produced a preliminary draft of guidelines that was reviewed at a second meeting the same year. A third meeting produced a report on mucositis pathophysiology, epidemiology, and treatment, including this report, will be published in the near future, as well as clinical practice guidelines.

**RESULTS:** Parallels created recommendations from higher levels of evidence and suggest that when evidence is of a lower level and there was a consensus regarding...
GUIDELINE CLASSIFICATION/HIERARCHY

• **Recommendation** A recommendation is reserved for guidelines that are based on Level I or Level II evidence

• **Suggestion** A suggestion is used for guidelines that are based on Level III, Level IV, & Level V evidence; this implies panel consensus on the interpretation of this evidence

• **No guideline possible** No guideline possible is used when there is insufficient evidence on which to base a guideline; this conclusion implies
  1) that there is little or no evidence regarding the practice in question or
  2) that the panel lacks a consensus on the interpretation of existing evidence.


CASE 1: ORAL MUCOSITIS

- AB is a 38 year old male
- History of Acute Lymphoblastic Leukemia (ALL), in complete remission (CR)

RECENT:
- Relapsed ALL
- Planned for
  - high dose chemotherapy (HDC)
  - total body irradiation (TBI)
  - stem cell transplantation (SCT) from donor
CASE 1: CASE HISTORY

• Past medical history
  – Moderate hypertension, controlled with ACE inhibitor
  – No other systemic abnormalities or medicines
  – No known allergies

• Social
  – Smoking: 1 pack/day for 8 years, quit 15 years ago
  – Alcohol: 2 glasses wine/day, less since diagnosis
  – Married
  – Computer programmer for 15 years
CASE 1: INDUCTION CHEMOTHERAPY

- Diagnosed October, 2000 with ALL

- Induction chemotherapy (vincristine; prednisone; asparaginase; daunorubicin; cyclophosphamide); CR
CASE 1: POST-REMISSION CHEMOTHERAPY

- Postremission consolidation, continuation and reinduction chemotherapy (6-mercaptopurine; vincristine; prednisone; daunorubicin; methotrexate) for two years

- Relapse October 2003
CASE 1: INDUCTION CHEMOTHERAPY
- Oral Health

• Prior to induction chemotherapy October 2000, latest dental examination 2 years earlier

• No apparent oral concerns
CASE 1: INDUCTION CHEMOTHERAPY
-Toxicity

- Toxicity history from induction chemotherapy
  - Short episode of gingival bleeding
  - Bad mouth ulcers
  - Oral pain
  - Nausea
  - Vomiting
  - Diarrhea
  - 10 kg weight loss
WHO ORAL MUCOSITIS SCALE

- Rates overall status
- Combines mucosal appearance, symptoms, functions
  - Grade 0: no changes
  - Grade 1: soreness/erythema
  - Grade 2: “ + ulceration / solid foods
  - Grade 3: “ / liquid diet
  - Grade 4: “ / oral alimentation not possible
WHO ORAL MUCOSITIS SCALE

- Grade 0: No changes

- Grade 1: Soreness/erythema

- Grade 2: + ulceration / solid foods

- Grade 3: / liquid diet

- Grade 4: / alimentation not possible
ORAL MUCOSITIS

Mucosal injury
- erythema
- edema
- ulcerations
- soreness, pain
ORAL MUCOSITIS

Mucosal injury
- erythema
- edema
- ulcerations
- soreness, pain

Thrombocytopenia

Salivary gland disturbances

Immuno-suppression

Disturbed microbial homeostasis
ORAL MUCOSITIS

- Salivary gland disturbances
- Thrombocytopenia
- Immuno-suppression
- Bleeding
- Xerostomia
- Mucosal injury
- Disturbed microbial homeostasis
- Virus infection
- Fungal infection
- Bacterial infection
GVHD

- Acute GVHD can cause oral ulceration
- Onset - Day 18-19
CASE 1: ALL RECURRENCE

• Relapsed ALL, treatment October, 2003:
  
  • Myeloablative conditioning regimen
    – fractioned 1335 cGy TBI
    – HDC (cyclophosphamide)
  
  • Allogeneic HSCT from a matched unrelated donor
GUIDELINES
- Mucositis Incidence

• WHAT IS THE RISK OF DEVELOPING ORAL MUCOSITIS?
  – Almost 100%

• WHAT IS THE RISK OF DEVELOPING GASTRO-INTESTINAL (GI) MUCOSITIS?
  – Almost 100%
GUIDELINES
- Oral Mucositis Incidence

• HDC + HSCT
  – Oral mucositis incidence near 100% for any grade
  – 30-50% Grade 3 and 4 oral mucositis without TBI
  – >60% Grade 3 and 4 oral mucositis with TBI

• Previous history of bad mucositis is not a clear predictor of subsequent mucositis
GUIDELINES
- Oral Mucositis Risk Factors

• WHAT ARE THE RISK FACTORS OF ORAL MUCOSITIS?
• Type and dose of chemotherapy
• Radiation to head and neck
• TBI
• Genetics
GUIDELINES
- Costs

• WHAT IS THE LIKELY COST OF GETTING OM/GIM?

• Non-transplant chemotherapy
  – With grade 3 or 4 oral mucositis:
    35% require dose delays
    60% require dose reduction
    30% have cessation of chemotherapy
  – With standard dose chemo and grade 3 or 4 oral mucositis:
    60% have fever and 62% require hospitalization
  – With high dose chemo and grade 3 or 4 oral mucositis:
    80% requiring opioid analgesics

• COST: $5,565/cycle
GUIDELINES - Costs

• High dose chemo and transplant
  – If develop oral ulceration:
    Require 5.8 additional days of narcotics
    Require 1.9 additional days of TPN
  – Oral mucositis associated with ↑ systemic infection and ↑ fatigue
  – ↑ of supportive care = ↑ need intensive nursing care, medical and dental specialist

• COST: $42,749
GUIDELINES
- Foundations of Care

• WHAT ORAL/DENTAL PREPARATION PRIOR TO ALLOGENEIC TRANSPLANT?

• GUIDELINE:

• Oral care protocols that include patient education is suggested in an attempt to reduce the severity of mucositis from chemotherapy or radiotherapy
NO GUIDELINES
- Foundations of Care (contin.)

• Not possible to provide guidelines for basic oral care related to mucositis, due to lack of clinical trials

• Yet, important to maintain mucosal health, reduce risk of ...

- bleeding
- dry mouth
- trauma or irritation symptoms of pain
- local infection
- disseminated infection
• Promote mucosal moisturization and protection

• Mouth care regimens
  – Tooth brushing with ultrasoft toothbrush
  – Bland rinses, e.g. normal saline, sodium bicarbonate rinses (cleans mucosal surfaces of thick secretions and debris, moisturizes, helps with oral comfort)
CASE 1: post HDC and allogeneic HSCT

• Patient develops grade 2 oral mucositis 4 days after transplant
• Can eat solid foods
• Rates pain as a 4 on 1-10 scale
NO GUIDELINES  
- Topical Anesthetics

• HOW SHOULD PATIENT BE MANAGED?

• No recommendations for use of topical anesthetics  
  - lack of well designed trials

• Topical anesthetics reasonable for mild/moderate and 
  breakthrough pain management  
  - needs further evaluation

• Check that the patient eats
CASE 1: post HDC and allogeneic HSCT

- Patient progresses to grade 4 oral mucositis day 7 post transplant
- TPN
- Rates pain as a 10 on 1-10 scale
HOW SHOULD PATIENT BE MANAGED?

GUIDELINE:

- Systemic patient-controlled analgesia (PCA) with morphine
NO GUIDELINES
- Continue Assessment of Oral Conditions

• Check for fungal, bacterial or virus infections that demand treatment

>Bacterial infection
  - E. coli
  - Pseudomonas

>Fungal infection
  - Candida albicans

>Virus reactivation
  - Herpes simplex
NO GUIDELINES
- Nutrition

• HOW SHOULD NUTRITION BE MAINTAINED?

• Naso-gastric feeding is preferable to total parental nutrition (TPN)
  - Less cost
  - Stimulates the GI mucosa
  - Lower complication rate
NO GUIDELINES
- Malnutrition

• WHAT IS THE RELATIONSHIP OF MALNUTRITION TO MUCOSITIS?
  – Grade 3 and 4 reduce ability to eat, with ↑ risk of malnutrition
  – With SDC: 70% of patients with grade 3 or 4 oral mucositis will require feeding tubes to maintain adequate nutrition
  – With HDC: 87% require feeding tubes

• Malnutrition recognized as a poor prognostic factor in cancer therapy
SUMMARY

- Mucosal alteration associated with chemo- and radiotherapy is multifactorial
- Many clinical studies failed to meet current standards
- MASCC/ISOO GUIDELINES demonstrate few preventive and treatment options for mucositis
- Further research necessary
  - Pathophysiology
  - Epidemiology
  - Therapy
CASE 2: GASTROINTESTINAL MUCOSITIS

• FG is a 56 year old man
• Diagnosed with Dukes’ C ca colon in 1997
  – No family history
• Medication: Ranitidine (stress-induced reflux)
• Runs a small Business
• Non-smoker
• ½ bottle wine per day
TREATMENT

• Sigmoid colectomy
  – Post operatively normal bowel actions

• 6 cycles 5-fluorouracil and folinic acid
  – Mayo regimen
  – 5-FU 375mg/m2/d and FA 20mg/m2/d D1-5, q28

• By day 5 C1
  – Moderate diarrhoea
  – Worsening epigastric pain
QUESTIONS

1. What is the diagnosis?
2. How do we grade the diarrhoea?
3. How do we grade the epigastric pain?
4. What are his risk factors for GIM?
5. What do the guidelines tell us about treating his diarrhoea?
6. What do the guidelines tell us about treating the epigastric pain?
7. What do we do for the next cycle?
WHAT IS THE DIAGNOSIS?
WHAT IS THE DIAGNOSIS?

- Gastrointestinal mucositis
  - Oesophageal
  - Small intestinal
  - Colonic
HOW DO WE GRADE THE DIARRHOEA?
HOW DO WE GRADE THE DIARRHOEA?

• NCI/CTC grading system

• Using the NCI/CTC diarrhoea grading system, moderate diarrhoea is an increase of 4-6 stools per day over normal, or nocturnal defaecation
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of &lt;4 stools / day over pre-treatment</td>
</tr>
<tr>
<td>2</td>
<td>Increase of 4-6 stools / day, or nocturnal stools</td>
</tr>
<tr>
<td>3</td>
<td>Increase of 7 or more stools / day, or incontinence; or need for parenteral support for dehydration</td>
</tr>
<tr>
<td>4</td>
<td>Requiring intensive care; or haemodynamic collapse</td>
</tr>
</tbody>
</table>
HOW DO WE GRADE THE EPIGASTRIC PAIN?
## HOW DO WE GRADE THE EPIGASTRIC PAIN?

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dyspepsia / Heartburn</th>
<th>Dysphagia / oesophagitis / odynophagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>Mild dysphagia, but can eat regular diet</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Dysphagia requiring pureed, soft or liquid diet</td>
</tr>
<tr>
<td>3</td>
<td>severe</td>
<td>Dysphagia requiring iv hydration</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>Complete obstruction-Cannot swallow saliva Or perforation</td>
</tr>
</tbody>
</table>
WHAT ARE HIS RISK FACTORS FOR GIM?
WHAT ARE HIS RISK FACTORS FOR GIM?

- Reflux
- Chemotherapy
WHAT DO THE GUIDELINES TELL US ABOUT TREATING THE DIARRHOEA?
WHAT DO THE GUIDELINES TELL US ABOUT TREATING THE DIARRHOEA?

- Loperamide
- Remove exacerbating foods from diet
- If loperamide fails
  - Octreotide
WHAT DO THE GUIDELINES TELL US ABOUT TREATING THE EPIGASTRIC PAIN?
WHAT DO THE GUIDELINES TELL US ABOUT TREATING THE EPIGASTRIC PAIN?

- Ranitidine
- Omeprazole
WHAT DO WE DO FOR THE NEXT CYCLE?
WHAT DO WE DO FOR THE NEXT CYCLE?

• Continue ranitidine or omeprazole throughout

• Add loperamide at 1st hint of diarrhoea

• Continue to avoid exacerbating foods

• If diarrhoea worsens
  – Consider dose reduction +/or delay
2001. re-presented with liver metastases

Treated with capecitabine (1.25g/m² bd. D1-14 q 21)

Restarted on omeprazole. Did not suffer oesophagitis

Major toxicities
- Diarrhoea
- Hand-foot syndrome

After 25% dose reduction, toxicities manageable with
- Loperamide
- Pyridoxine
10 months later, liver metastases progressed
Switched to FOLFOX (5FU, folinic acid and Oxaliplatin)

- Diarrhoea controlled with loperamide
- Cold-sensitive neuropathy

Good response
Treatment stopped after 6 cycles (12 doses)
January 2004 (10 months off treatment)

Progressive Disease again
- Treated with single agent Irinotecan

Omeprazole continued

Atropine premedication

Loperamide at 1st hint of diarrhoea
• Developed Grade 4 diarrhoea

• Hospitalised with
  – Fever
  – Diarrhoea
  – Weight-loss
  – Cramping abdominal pain

• Diarrhoea persisted despite maximum dose loperamide (11 per day)

• Became neutropaenic

• AXR: oedematous bowel wall, multiple distended bowel loops, and fluid levels.
• Treated with
  – Intravenous fluids
  – Antibiotics
  – Loperamide
  – Octreotide
  – G-CSF
  – Morphine

• Very slow recovery!
WE NEED BETTER TREATMENT FOR GIM!
SUMMARY (MOTHERHOOD) QUESTIONS

1. How do we get a nursing protocol that addresses the guidelines?
2. How do we get a dental plan that is based on the evidence?
3. Given how little we can actually do to help now, how can we work towards fixing mucositis for the future?
4. What trials should we be doing, and what would the ideal protocol be?
FINAL ANSWERS

- Review our institutional protocols with the guidelines in our hands.
  - Question everything in them
  - Make sure we are not doing anything un-necessary, or even detrimental!

- We need to do ongoing
  - Basic research into mechanisms and treatment
  - Epidemiological and clinical research into risk factors and burden of care
  - Clinical studies of newer, more promising agents

- And the studies need to be well-designed!
Future Plans

• Update of guidelines will occur in next year
  – And there are some exciting new agents!

• Professional and Patient education
  – Next year in Geneva
  – Dissemination of guidelines

• MASCC website
  – Mucositis section development

• Research Plans
  – Burden of care