Assessment and Grading of Oral Mucositis after Stem Cell Transplantation

Corey Cutler, MD MPH FRCP(C)
Dana-Farber Cancer Institute
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Stomatitis

A fish hook lodges in my throat.
Spittle, kindergarten paste, thickens everything – even vision.
Mouth, pocked with sores & blisters, swollen ulcerated tongue.
Topside, sandpapered with number 7 coarsest grade.
Taste buds, saliva glands, seared.
Cool water, corrosive acid now.
The tongue rests; teeth become enemies.
Coiled steel razored wire atop dentate prison walls.
Only moans escape my lips. I cannot eat or speak.
Inside a howl festers.
Pain lengthens time.

Anita Hart Balter

Oral Mucositis

♦ Side Effect of Standard Cytotoxic Chemotherapy
- Effect on tissues with rapid cell turnover
  - Bone Marrow - Myelosuppression
  - Hair Follicles - Alopecia
  - GI system - Diarrhea
  - - - Esophagitis
  - - - Oral mucositis
Close to 400,000 Patients Per Year Suffer From Mucositis During Cancer Therapy

- Colorectal 21%
- Breast 14%
- Stem Cell Transplant 4%
- NHL 5%
- NSCLC 41%
- Head and Neck 15%

Source: Mattson Jack Database 2003; NCI; Note: 400,000 patients in the US

Oral Mucositis: The Worst Complication of Myeloablative Transplantation

- Most Debilitating Side Effects
- Oral Mucositis
- Nausea and Vomiting
- Weakness and Lethargy
- Diarrhea


For Every 55 Patients with Severe Mucositis and Myelosuppression...

- 41 will develop infection
- 5 will die.

Elting, et al; Cancer 2003
Relationship of Mucositis to Outcomes in BMT

<table>
<thead>
<tr>
<th>Health Outcome</th>
<th>Increase in Days: Mucositis vs. No Mucositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable narcotics</td>
<td>4.80 (&lt;0.01)</td>
</tr>
<tr>
<td>TPN days</td>
<td>5.34 (&lt;0.01)</td>
</tr>
<tr>
<td>Febrile days</td>
<td>1.59 (&lt;0.02)</td>
</tr>
<tr>
<td>Significant infection</td>
<td>2.55 (&lt;0.05)</td>
</tr>
<tr>
<td>Hospital days (autos)</td>
<td>11.02 (&lt;0.01)</td>
</tr>
<tr>
<td>Hospital days (allos)</td>
<td>6.92 (&lt;0.02)</td>
</tr>
</tbody>
</table>

Pathobiology of Mucositis

Clinical Features of Mucositis
- Erythema
- Ulceration
- Pseudomembrane formation
- Consequences
  - Pain
  - Difficulty in swallowing/chewing food
    - Decreased nutrition
    - Requirement for IV nutrition
  - Infectious risk
    - Breakdown of mucosal barrier
    - Risk of bacteremia secondary to TPN
Reasons to ‘Measure’ Mucositis

♦ Toxicity description and assessment
♦ Medical management
♦ Research
  – Descriptive studies
  – Intervention studies

Ideal Mucositis Scale

♦ Accurately reflects severity and course of objective and subjective clinical changes.
♦ Easy to teach and use, with minimal inter-observer variability.
♦ Does not require lesion measurement.
♦ Sensitive enough to discriminate treatment efficacy.
♦ Clinically meaningful and easily interpretable end points for clinicians, patients, and FDA.

Mucositis Research Instruments

♦ No uniformity in end points.
♦ Wide range of complexity.
♦ Provide tight, comparable data, but meaningfulness of end points may be difficult to convey in general clinical settings, ie. How important is a difference between 1.62 vs. 0.77?
♦ Major value in phase 2 trials and outcome analyses, but of limited value in phase 3 trials.
Mucositis Scale Frequency

- WHO
- NCI CTC
- Undefined
- Collaborative study
- RTOG
- Bearman
- Other

Mucositis Scales to be Reviewed

- WHO Oral Toxicity Scale (WHO Score)
- NCI-CTC v3 Mucositis Scale
  - Clinical Score
  - Functional/Symptomatic Score
- OMAS

WHO Score

- Based on a combination of subjective, objective and functional outcomes:
  - Subjective – Soreness as described by the patient
  - Objective – Presence of erythema and ulcerations
  - Functional – Ability to eat solids, liquids or nothing by mouth
**WHO Score**

- Grade 0 – No objective findings, function irrelevant
- Grade 1 – Erythema plus pain, function irrelevant
  - May include mucosal scalloping with or without erythema or soreness
- Grade 2 – Ulceration, ability to eat solids
- Grade 3 – Ulceration, ability to eat liquids
- Grade 4 – Ulceration, nothing by mouth

**WHO Oral Mucositis Scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>None</th>
<th>Soreness +/- erythema</th>
<th>Ulceration, ability to eat solids</th>
<th>Ulceration, extensive erythema</th>
<th>Ulcers, extensive erythema to the extent that alimentation is not possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diet Assessment – Food Definitions**

- **Solids**
  - Foods that have to be chewed
  - Chunky soups, meats, grains, pasta or whole vegetables
- **Liquids**
  - Foods that take the shape of their container
  - Pureed soups, Jell-O®, pudding, mashed potatoes, baby food, Ensure® or other liquid supplement
- **Nothing Per Os**
  - No eating or drinking, except enough liquid to allow for taking of medications
**WHO Scale Grading Nuances**

- Pain in the absence of objective findings = 0
- Erythema without pain = 0
- Ulcers, automatically ≥ 2
- Extent or size of ulcers is not a driver

**WHO Grading Tips**

- **Grade 1**: If there is an ulcer, it’s not Grade 1: May include mucosal scalloping with or without erythema or soreness.
- **Grade 2**: Can’t be a Grade 2 unless there is an ulcer. Solid diet.
- **Grade 3**: Ulcers. Liquid diet. No solids.
- **Grade 4**: Mucositis of such severity that eating/drinking is impossible. PO meds don’t count

**WHO Grading Examples**

- Subject has a fentanyl patch, large ulceration, no erythema, can eat Jello® and pudding: 4
- Subject is taking an NSAID (within the last 24 hrs) for mouth pain, is now not sore and has erythema: 0
- Subject has no erythema, no soreness, can eat solids and has an ulcer: 2
- Subject has severe erythema, mouth pain and can only tolerate liquids: 1
### NCI-CTC v3 Scoring

- **Two Components**
  1. Clinical Score – Objective findings
  2. Functional/Symptomatic Score – Functional findings

### CTC Clinical Score

- 0 = No oral mucositis
- 1 = Erythema
- 2 = Patchy ulceration or pseudomembrane formation
- 3 = Confluent ulceration or pseudomembrane, confluent ulceration occupies >50% of the mucosal surface of the designated anatomic site
- 4 = Tissue necrosis

### CTC Functional/Symptomatic Score

- 1 = Ability to eat solids
- 2 = Requires liquid diet
- 3 = Not able to tolerate a solid or liquid diet
- 4 = Symptoms associated with life-threatening consequences

**NOTE:** If diet is limited for reasons other than mucositis, the CTC Functional/Symptomatic Score is based on what the subject feels he/she could eat.
Anatomic Site-Directed Scoring

- Inner aspect of upper lip
- Inner aspect of lower lip
- Right cheek mucosa
- Left cheek mucosa
- Right bottom and side of tongue
- Left bottom and side of tongue
- Floor of mouth and frenulum
- Soft palate

Oral Mucositis Assessment Scale (OMAS)

<table>
<thead>
<tr>
<th>Location</th>
<th>OMAS Score</th>
<th>OMAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner aspect of upper lip</td>
<td>0 1 2 3 5</td>
<td></td>
</tr>
<tr>
<td>Inner aspect of lower lip</td>
<td>0 1 2 3 5</td>
<td></td>
</tr>
<tr>
<td>Right cheek mucosa</td>
<td>0 1 2 3 5</td>
<td></td>
</tr>
<tr>
<td>Left cheek mucosa</td>
<td>0 1 2 3 5</td>
<td></td>
</tr>
<tr>
<td>Right bottom and side of tongue</td>
<td>0 1 2 3 2</td>
<td></td>
</tr>
<tr>
<td>Left bottom and side of tongue</td>
<td>0 1 2 3 2</td>
<td></td>
</tr>
<tr>
<td>Floor of mouth and frenulum</td>
<td>0 1 2 3 5</td>
<td></td>
</tr>
<tr>
<td>Soft palate</td>
<td>0 1 2 3 5</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0 1 2 3 3</td>
<td></td>
</tr>
</tbody>
</table>

*Severity Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe

Correlations Between Peak OMAS Score and Selected Clinical and Economic Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile days</td>
<td>0.13</td>
</tr>
<tr>
<td>Sig infection</td>
<td>0.26*</td>
</tr>
<tr>
<td>TPN days</td>
<td>0.39*</td>
</tr>
<tr>
<td>Injectable-narcotic days</td>
<td>0.36*</td>
</tr>
<tr>
<td>Total hospital days</td>
<td>0.28*</td>
</tr>
<tr>
<td>Total hospital charges</td>
<td>0.48*</td>
</tr>
</tbody>
</table>
How Frequently Should Evaluations Be Done?

- Depends on the reason for the assessment.
- Mucosal condition in chemotherapy responds relatively acutely.
- Consequently, accuracy of assessment tracks well with frequency of evaluation.
- Since duration of significant mucositis is the most important driver of untoward outcomes of mucositis, less than daily assessment is risky, especially in clinical trials.

Why Does Mucositis Matter

- BMT CTN 0401 – Will intervention make mucositis worse???
- BMT CTN 0402 – Will intervention make mucositis better???
- New interventions exist - Palifermin

0401: Bexxar-BEAM vs BEAM

- Autologous transplantation – standard for relapsed non-Hodgkin’s Lymphoma
  - Usual regimen: High-dose chemotherapy – BEAM or equivalent.
  - 0401 – Tests hypothesis that the addition of \(^{131}I\)-Tositumomab to high-dose chemotherapy will increase response rate \(\rightarrow\) survival
  - BUT: Addition of radio-immunotherapy may increase mucositis
Pathobiology of Mucositis

<table>
<thead>
<tr>
<th>Normal Epithelium</th>
<th>Phase I Initiation</th>
<th>Phase II &amp; III Messaging, Signaling, &amp; Amplification</th>
<th>Phase IV Ulceration (Mucositis)</th>
<th>Phase V Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submucosa</td>
<td>Radiation</td>
<td>Bacteria</td>
<td>Blood Vessel</td>
<td>Epithelial Layer</td>
</tr>
<tr>
<td>Epithelial Layer</td>
<td>Chemotherapy</td>
<td></td>
<td>Inflammatory Cell</td>
<td>Fibroblast</td>
</tr>
</tbody>
</table>

0402: Effect of Methotrexate Elimination

  - Cohorts designated by GVHD prophylaxis:
    - Sirolimus/Tacrolimus vs. Tacrolimus/Methotrexate
    - Cy-TBI MRD PBSCT
  - Oral Mucositis
    - Mucositis assessed 2-3x/week by members of the Oral Medicine service
    - OMAS scale

Other Outcomes

- Total Parenteral Nutrition
  - Total number of days of use recorded

- Narcotic use
  - Conversion of all narcotics to intravenous mg morphine equivalents (MME) using accepted conversion factors

- Duration of Hospitalization
  - From day of transplantation to 1st discharge
<table>
<thead>
<tr>
<th>Data</th>
<th>Siro / Tacro</th>
<th>Tacro / Mtx</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>30</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Median Age</td>
<td>42 (19-54)</td>
<td>43 (24-58)</td>
<td>0.46</td>
</tr>
<tr>
<td>Male Gender</td>
<td>16 (53%)</td>
<td>11 (46%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML/MDS</td>
<td>15 (50%)</td>
<td>16 (67%)</td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td>7 (23%)</td>
<td>3 (13%)</td>
<td></td>
</tr>
<tr>
<td>NHL/ALL</td>
<td>8 (27%)</td>
<td>5 (21%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Time To ANC &gt; 500</td>
<td>14 (11-17)</td>
<td>15 (11-25)</td>
<td>0.04</td>
</tr>
<tr>
<td>Gr II-IV GVHD</td>
<td>3 (10%)</td>
<td>6 (25%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessments</td>
<td>5</td>
<td>6.5</td>
<td>0.36</td>
</tr>
</tbody>
</table>

### Mucositis Incidence

<table>
<thead>
<tr>
<th>Peak Mucositis Score</th>
<th>Mucositis Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>2-3</td>
<td>30 (20%)</td>
</tr>
<tr>
<td>4-5</td>
<td>40 (25%)</td>
</tr>
</tbody>
</table>

### Duration of Mucositis

<table>
<thead>
<tr>
<th>Duration of Ulcerative Mucositis (days)</th>
<th>ST group</th>
<th>TM group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TPN usage

<table>
<thead>
<tr>
<th>Patients Requiring TPN(%)</th>
<th>ST group</th>
<th>TM group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p = 0.08</td>
<td></td>
</tr>
</tbody>
</table>

### Days of TPN required

<table>
<thead>
<tr>
<th>Duration of TPN Usage</th>
<th>ST group</th>
<th>TM group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| p = 0.005             |          |          |

| p = 0.0002            |          |          |

| p = 0.08              |          |          |
**Narcotic Utilization**

![Narcotic Utilization Graph]

- Total MME: 0
- MME/Day: 200
- MME/Narcotic Day: 800

**Duration of Hospitalization**

- ST group: 30 days
- TM group: 40 days

**Methotrexate Conclusions**

- GVHD prophylaxis with Sirolimus-Tacrolimus is associated with less oral mucositis than with a Methotrexate-containing regimen.
- Patients who do not receive Methotrexate require less TPN and less narcotics.
- Hospitalization duration is shortened in patients not treated with Methotrexate.
- The improved mucositis outcomes with non-Methotrexate containing regimens may be associated with substantial cost savings.
Prevention of Oral Mucositis

♦ “Many are called, but few are chosen”
  – Multiple agents failed in randomized trials;
  – Until recently, no standard
♦ Palifermin
♦ Velafermin

Palifermin

♦ The mouth is covered in specialized epithelium called keratinocytes
♦ Palifermin is a recombinant N-terminal truncated version of Keratinocyte Growth Factor (KGF) with same biological activity but increased stability
♦ KGF is a 28kD, heparin-binding member of the fibroblast growth factor family
♦ Ameliorates mucositis in murine model

Palifermin-Induced Thickening of Normal Tongue Mucosa

Ventral surface of rodent tongue mucosa in absence or presence of palifermin (rHuKGF) 5 mg/kg/day for 3 days
**Palifermin**

- Phase I (Meropol et al, JCO 1993):
  - Doses of 80 ug/kg x 3 d appeared safe
- Phase II (Sonis et al, Cancer 1995)
  - Etoposide, Cytarabine, Melphalan preparative regimen
  - Reduced mucositis and weight loss
- Phase III (Spielberger et al, NEJM 2004)
  - Palifermin vs. placebo in XRT-containing preparative regimen for autologous transplant

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**Palifermin vs. Placebo - Design**

- **Inclusion**
  - > 18 yo
  - KPS ≥ 70%
  - Autotransplant planned for heme malignancy
- **Treatment**
  - Etoposide/Cytoxan/TBI preparative regimen
  - Palifermin @ 60 ug/kg x 3d iv prior to XRT
  - Palifermin @ 60 ug/kg x 3d iv d0, 1, 2
  - Double blind
  - G-CSF given from d0 to recovery

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**Palifermin vs. Placebo - Endpoints**

- Mucositis assessment daily, multiple scales
  - WHO
  - RTOG
  - WCCNR
- Patient-reported outcomes
  - Sore throat
  - ADL participation
- Narcoitic use
- TPN use
- Primary endpoint: duration of WHO gr3/4 mucositis
Palifermin vs. Placebo - Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Palifermin Group (n=106)</th>
<th>Placebo Group (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%)</td>
<td>59 (55)</td>
<td>72 (68)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Range</td>
<td>58-69</td>
<td>58-68</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>21 (20)</td>
<td>25 (24)</td>
</tr>
<tr>
<td>Hodgkin's Disease</td>
<td>11 (11)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Leukemia (%)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

<medicalnotation>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Palifermin (n=106)</th>
<th>Placebo (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (y)</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Range</td>
<td>58-69</td>
<td>58-68</td>
</tr>
</tbody>
</table>


Palifermin vs. Placebo - Results

Incidence of Oral Mucositis (%)

- Grade 0
  - Palifermin (n=106)
  - Placebo (n=106)
- Grade 1
- Grade 2
- Grade 3
- Grade 4

63% 3d
98% 9d


Palifermin vs. Placebo – Patient-Reported Outcomes

- Mean Score for Quality of Life and Health Outcomes
  - Palifermin
  - Placebo

Palifermin vs. Placebo - Results

- Lower dose of opioids administered (morphine equivalents): 212 vs. 535 mg
- Lower duration of opioid administration: 7 vs. 11d
- Lower incidence of febrile neutropenia: 75 vs. 92%
- Lower incidence of blood-borne infections: 15 vs. 25%
- Lower incidence of TPN use: 31 vs. 55%

Palifermin vs. Placebo - Safety

- Rarely discontinued
- Most events with > 5% frequency in palifermin group (and not in placebo group) were due to effect of drug on skin and oral epithelium
- SAE: Rash; Hypotension
- Deaths: 1 in each group
- 12 month PFS is similar in both groups
- No excess of cancer deaths in either group (ie KGF does not protect tumors)

Palifermin vs. Placebo - Conclusions

- Palifermin was effective in reducing the incidence and duration of severe and life-threatening mucositis
- Reduction in opioid and TPN use probably beneficial for pts
- Other Questions:
  - Role in Allo transplant – not effective as GVHD prophylaxis
Velafermin

- Recombinant Human Fibroblast-Growth Factor-20
- Promotes Epithelial and Mesenchymal cell proliferation – prevents mucositis in animal models
- Being tested in Ph II trials in people undergoing autologous transplantation

**Velafermin Trial**

Schuster et al, ASCO 2006

**Velafermin – Patient Population**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Velafermin (mg/Kg)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.03</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender - n (%)</td>
<td>(N=51)</td>
<td>(N=50)</td>
</tr>
<tr>
<td>Male</td>
<td>25 (55%)</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (43%)</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>Age - y</td>
<td>Median Range</td>
<td>53-71</td>
</tr>
<tr>
<td></td>
<td>(N=51)</td>
<td>(N=50)</td>
</tr>
<tr>
<td>Diagnosis - n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALT</td>
<td>6 (12%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>NL</td>
<td>10 (20%)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>MM</td>
<td>32 (62%)</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>AML</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>49 (96%)</td>
<td>47 (94%)</td>
</tr>
<tr>
<td>CT + TBI</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

Schuster et al, ASCO 2006
**Velafermin - Outcomes**

*Non-Dose Dependent Pharmacology suggested in animal studies*  
Schuster et al, ASCO 2006

- Primary Endpoint not met in this trial
- Safety established
- Further studies planned at optimal dose

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**Velafermin**

- Primary Endpoint not met in this trial –
- Safety established
- Further studies planned at optimal dose

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**Summary**

- Mucositis - An important complication of myeloablative transplantation
- Scoring – Important for research and patient care
- New agents may change incidence and severity
- New agents may prevent mucositis – need to be tested further
• Acknowledgements
  – Nathaniel Treister, DMD
  – Stephen Sonis, DMD
  – Richard Stone, MD