Drug and Nutrition in Cancer Patient

By Nirachorn Kuchonthara RPh, BCOP, BCNSP, ThaiBCP
Outline

• Introduction

• Chemotherapy associated Toxicity
  – Nausea and Vomiting
  – Mucositis and Stomatitis
  – Constipation and Diarrhea
  – Anorexia and Cachexia
Nutritional therapy goals:

• Maintain weight and/or minimize weight loss
• Maintain visceral protein stores
• Maintain adequate hydration
• Promote normal bowel function
• Through oral intake or nutrition support, provide the majority of estimated nutrition needs on a daily basis
Risk for Malnutrition

• Malnutrition risk is identified through history and physical examination
• Laboratory data, anthropometrics, and patient history including body weight are important screening and assessment tools
World Cancer Burden 2012

Incidence

Cancer is a leading cause of disease worldwide. An estimated 14.1 million new cancer cases occurred in 2012.

1. Lung cancer
2. Female breast cancer
3. Colorectal cancer
4. Stomach cancer

Mortality

Cancer is a leading cause of death worldwide, with 8.2 million deaths in 2012. More than half of all cancer deaths each year are due to

1. Lung cancer
2. Stomach cancer
3. Liver cancer
4. Colorectal cancer
5. Female breast cancers
Gompertzian kinetics

Tumor growth curve

$10^9$ cell = 1 gm = diameter 1 cm
Treatment of cancer

1. Surgery
   - Diagnosis and treatment
   - Remove the tumor for localized treatment

2. Radiation
   - Localized treatment

3. Immunotherapy
   - Systemic treatment utilizing the host’s immune system
Treatment of cancer (cont.)

4. Chemotherapy
   - Systemic treatment
     • Neoadjuvant chemotherapy
       - Used to reduce tumor burden
       - Usually administered prior to surgery
     • Adjuvant chemotherapy
       - Eradicate micrometastases following localized treatment
       - Potentially curable disease
         » With no clinical detectable disease following surgery or radiation
5. Targeted therapy

- Angiogenesis inhibitors: Antiangiogenic TKIs (Sorafenib, Sunitinib, Pazopanib, Axitinib, Vandetanib, Regorafenib, Lenvatinib, etc), IMiDs, EGFR inh.
- Gene therapy (NK cell)
- Tumor vaccine
- Signal transduction inhibitor e.g. Imatinib (Gleevec®)
- Monoclonal antibodies: Rituximab (Rituxan®), Gemtuzumab, Trastuzumab, Bevacizumab, Ranibizumab, Afibercept, Ramucirumab
Goals for Monoclonal Antibodies

– Activity

• High specificity for a target critical to tumor growth and survival

• Able to achieve meaningful clinical benefit

– Utility

• Can be used as single agent or in combination

• Minimal overlapping toxicities

• Potential targets present across tumor types and stages of disease

### Therapeutic Options in Cancer

<table>
<thead>
<tr>
<th></th>
<th>Monoclonal Antibodies</th>
<th>Tyrosine Kinase Inhibitors</th>
<th>Chemotherapy</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity for a target</td>
<td>Absolute Specificity</td>
<td>Variable Specificity</td>
<td>Low Specificity</td>
<td>Low Specificity</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Low</td>
<td>Low/Moderate</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>MTD Evaluated*</td>
<td>Pending</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Administration</td>
<td>IV</td>
<td>IV/Oral</td>
<td>IV/Oral</td>
<td>Local</td>
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<tr>
<td>Half-life</td>
<td>Days to weeks</td>
<td>Hours to days</td>
<td>Hours to days</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Does not include radio-labeled or toxin-conjugated monoclonal antibodies

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Principles of chemotherapy

• Goal
  – Curative e.g. leukemias, lymphomas, testicular cancer
  – Inhibit cancer spread
  – Palliation
  – Optimal efficacy with minimal toxicity
## Chemosensitivity of tumors

### High
- ALL
- Hodgkin’s disease
- NHL
- Testicular Cancer
- SCLC
- Wilms’ tumor

### Medium
- Ovarian Cancer
- Breast Cancer
- Osteosarcoma
- Head and Neck cancer
- Multiple Myeloma
- Bladder cancer
- Colorectal cancer

### Low
- NSCLC
- Cervical cancer
- Endometrial cancer
- Adult soft tissue sarcoma
- Melanoma
- Liver cancer
- Gastric carcinoma
- Pancreatic cancer

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Mechanism of Action of some anticancer drugs

Purine Synthesis

Antimetabolites
- 6-Mercaptopurine
- 6-Thioquanine
- Methotrexate → DHFR

- Hydroxyurea
- 5-Fluorouracil
- Cytarabine
- Gemcitabine

Ribonucleotides

Ribonucleotide reductase

Deoxyribonucleotides

DNA

RNA

Proteins

Enzymes
Microtubules

Pyrimidine Synthesis

Alkylation agents
Alkylation → Alter structure & function of DNA by cross linking and/or fragmenting DNA

- Alkylating agents
- Antibiotics

- L-Asparaginase

Etoposide
Topoisomerase II Inhibitor-DNA break

Vinca Alkaloids → Prevent polymerization
Taxanes → Enhance polymerization

Enzymes

Site of Chemotherapy Action in Relationship to the Cell Cycle

**Cell cycle (Phase)**
- **Non-specific agents**
- **Alkylating Agents**
  - Chlorambucil
  - Cyclophosphamide
  - Ifosfamide
  - Bendamustine
  - Busulfan
  - Melphalan
- **Anthrycylines**
- **Antibiotics**
  - Doxorubicin
  - Epirubicin
  - Idarubicin
  - Mitoxantrone
- **Antitumor Antibiotics**
  - Dactinomycin
  - Mitomycin
  - Carmustine (BCNU)
- **Miscellaneous**
  - Altretamine
  - Carboplatin
  - Cisplatin
  - Dacarbazine
  - Oxaliplatin
  - Procarbazine

**Site of Action**
- **Mitotic index**
  - G1: 18-30 hrs
  - S: 16-20 hrs
  - G2: 2-10 hrs
  - M: 30-60 mins

**Phases**
- **Go** (Variable resting phase)
  - **Paclitaxel**
  - **Docetaxel**
  - **Cabazitaxel**
  - **Ixabepilone (G2/M)**
  - **Eribulin (G2/M)**
  - **Bleomycin (G2/M)**
  - **Etoposide (S/G2)**
  - **Irinotecan**
  - **Topotecan**
  - **VinBLASTine**
  - **VinCIРИSTine**
  - **VinORELBine**

**Lymphokines**
- (Ex. Interferon)
Chemotherapy
(Oral: Cytotoxic drugs)

- Alkeran® 2 mg (Melphalan)
- Endoxan® 50 mg (Cyclophosphamide)
- Hexalen® 50 mg (Altretamine)
- Myleran® 2 mg (Busulfan)
- Leukeran® 2 mg (Chlorambucil)
- Natulan® 50 mg (Procarbazine)
- Temodal® 20 mg, 100 mg (Temozolamide)
- Zavedos® 5 mg, 10 mg (Idarubicin)
- Etoposide® 50 mg
- Navelbine® 20 mg, 30 mg (VinORELBine)
Chemotherapy
(Oral: Cytotoxic drugs)

- Methotrexate 2.5 mg Tab.
- Fludara® 10 mg (Fludarabine)
- Puri-Nethol 50 mg (6-MP)
- Hydrea® 500 mg (Hydroxyurea)
- TS-1® 20 mg, 25 mg (Tegafur + Gimeracil + Oteracil potassium)
- Lonsurf® 15 mg, 20 mg (Trifluridine + Tipiracil)*
- UFUR (Tegafur + Uracil)
- Xeloda® 150 mg, 500 mg (Capecitabine)
Hormonal Agents

- Nolvadex D® 20 mg (Tamoxifen)
- Celvista® 60 mg (Raloxifene)
- Fareston® 60 mg (Toremifene)
- Megace® 160 mg (Megestrol acetate)
- Farlutal 500 mg (Medroxyprogesterone)
- Eligard® 22.5 mg (Leuprolide)
- Zoladex® LA Depot. 10.8 mg inj. (Gosereline)
<table>
<thead>
<tr>
<th>Hormonal Agents</th>
</tr>
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<tbody>
<tr>
<td>• Arimidex® 1 mg (Anastrozole)</td>
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<tr>
<td>• Femara® 2.5 mg (Letrozole)</td>
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<tr>
<td>• Aromasin® 25 mg (Exemestane)</td>
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<tr>
<td>• Casodex® 50 mg, 150 mg (Bicalutamide)</td>
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<tr>
<td>• Fugerel® 250 mg (Flutamide)</td>
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<tr>
<td>• Zytiga® 250 mg (Abiraterone)</td>
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<tr>
<td>• Xtandi® 40 mg (Enzalutamide)</td>
</tr>
<tr>
<td>• Lysodren® 500 mg (Mitotane)</td>
</tr>
</tbody>
</table>
Targeted Therapy

- Afinitor® 5 mg, 10 mg (Everolimus)
- Tarceva® 100 mg, 150 mg (Erlotinib)
- Iressa® 250 mg (Gefitinib)
- Gilotrif® 30 mg, 40 mg (Afatinib)
- Glivec® 100 mg (Imatinib)
- Sprycel® 50 mg (Dasatinib)
- Tasigna® 150 mg, 200 mg (Nilotinib)
- Sutent® 12.5 mg (Sunitinib)
- Nexavar® 200 mg (Sorafenib)
- Inlyta® 5 mg (Axitinib)
- Votrient® 200 mg, 400 mg (Pazopanib)
- Xalkori® 250 mg (Crizotinib®)
- Tykerb® 250 mg (Lapatinib)
- Stivarga® 40 mg (Regorafenib)
- Jakavi® 20 mg (Ruxolitinib)
- Thalidomide® 50 mg
- Revlimid® 5 mg, 10 mg, 15 mg, 25 mg (Lenalidomide)
Patient Perceptions of the Most Severe Side Effects of Cancer Chemotherapy

<table>
<thead>
<tr>
<th>Rank</th>
<th>1983¹</th>
<th>1993²</th>
<th>1995³</th>
<th>1999⁴</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Vomiting</td>
<td>Nausea</td>
<td>Nausea</td>
<td>Nausea</td>
</tr>
<tr>
<td>2.</td>
<td>Nausea</td>
<td>Constantly tired</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
</tr>
<tr>
<td>3.</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
<td>Vomiting</td>
<td>Constantly tired</td>
</tr>
<tr>
<td>4.</td>
<td>Thought of coming for treatment</td>
<td>Effect on family</td>
<td>Constantly tired</td>
<td>Vomiting</td>
</tr>
<tr>
<td>5.</td>
<td>Length of time treatment takes</td>
<td>Vomiting</td>
<td>Having to have an injection</td>
<td>Changes in the way things taste</td>
</tr>
</tbody>
</table>

Incidence of Emesis on Day 2 and 3 Following chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>FAC</th>
<th>CMF</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>40%</td>
<td>&gt;50%</td>
<td>25%</td>
<td>10%-20%</td>
</tr>
<tr>
<td>Day 3</td>
<td>61%</td>
<td>&lt;20%</td>
<td>&lt;10%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

FAC = 5-fluorouracil, Adriamycin (doxorubicin), and cyclophosphamide; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; NA = data not available
### Central Nervous System
- Cortex
- Thalamus
- Hypothalamus
- Meninges

### Vestibular System
- H<sub>1</sub> receptor?
- M<sub>1</sub> receptor

### Gastrointestinal Tract and Heart
- Mechanoceptors
- Chemoreceptors
- 5-HT<sub>3</sub> receptor

### Fourth Ventricle
- Chemoreceptor trigger zone

### Chemoreceptor Trigger Zone (Area Postrema)
- Chemoreceptors
- D<sub>3</sub> receptor
- NK<sub>1</sub> receptor?
  - (5-HT<sub>3</sub> receptor)

### Vomiting Center (Nucleus of Tractus Solitarius)
- H<sub>1</sub> receptor
- M<sub>1</sub> receptor
- NK<sub>1</sub> receptor?
  - (5-HT<sub>3</sub> receptor)

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Neurotransmitters/Treatments Associated With Emesis

- Dopamine/Dopamine Receptor antagonists
- Histamine
- Serotonin/5-HT3 Receptor antagonists
- Endorphins
- Substance P/NK-1 Receptor antagonists
- Acetylcholine
- GABA
- Cannabinoids
Oncologists and Nurses Predictions of the Incidence of Chemotherapy-Induced Nausea and Vomiting VS Actual Incidence in Patients Receiving a Highly Emetogenic Chemotherapy Regimen for Cancer

Healthcare providers' predictions of incidence, and observed incidence, of nausea and vomiting following chemotherapy.


<table>
<thead>
<tr>
<th>Level</th>
<th>IV Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Emetic Risk</strong>&lt;br&gt;(Level 5)&lt;br&gt;(&gt;90% frequency of emesis)</td>
<td>- AC or EC combination&lt;br&gt;- Cisplatin&lt;br&gt;- Cyclophosphamide &gt; 1500 mg/m²&lt;br&gt;- Carmustine ≥ 250 mg/m²&lt;br&gt;- Dacarbazine&lt;br&gt;- Mechlorethamine&lt;br&gt;- Streptozocin&lt;br&gt;- Doxorubicin &gt; 60 mg/m²&lt;br&gt;- Epirubicin &gt; 90 mg/m²&lt;br&gt;- Ifosfamide ≥ 10 Gm/m² (≥2 Gm/dose)</td>
</tr>
<tr>
<td>Level</td>
<td>IV Agent</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Moderate Emetic Risk</strong></td>
<td>- Aldesleukin &gt;12–15 million IU/m²</td>
</tr>
<tr>
<td>(Level 3-4)</td>
<td>- Arsenic trioxide</td>
</tr>
<tr>
<td>(30-90% frequency of emesis)</td>
<td>- Azacitididine</td>
</tr>
<tr>
<td></td>
<td>- <em>Oxaliplatin</em></td>
</tr>
<tr>
<td></td>
<td>- Cytarabine &gt; 200 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- <em>Carboplatin</em></td>
</tr>
<tr>
<td></td>
<td>- Carmustine ≤ 250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- Ifosfamide &lt; 2 Gm/m²/dose</td>
</tr>
<tr>
<td></td>
<td>- Cyclophosphamide &lt; 1,500 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- Idarubicin</td>
</tr>
<tr>
<td></td>
<td>- Epirubicin ≤ 90 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- Doxorubicin ≤ 60 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- <em>Irinotecan</em></td>
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<tr>
<td></td>
<td>- Busulfan</td>
</tr>
<tr>
<td></td>
<td>- Melphalan</td>
</tr>
<tr>
<td></td>
<td>- Dactinomycin</td>
</tr>
<tr>
<td></td>
<td>- Methotrexate ≥ 250 mg/m²</td>
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<tr>
<td></td>
<td>- Clofarabine</td>
</tr>
</tbody>
</table>
**Emetogenic Potential of Chemotherapy Agents**

<table>
<thead>
<tr>
<th>Level</th>
<th>IV Agent</th>
</tr>
</thead>
</table>
| **Low Emetic Risk** (10-30% frequency of emesis) | - Ado-trastuzumab emtansine  
- Aldesleukin ≤12 million IU/m²  
- Amifostine ≤300 mg/m²  
- Brentuximab vedotin  
- Cabazitaxel  
- Carfilzomib  
- Cytarabine (low dose) 100–200 mg/m²  
- **Docetaxel**  
- Doxorubicin (liposomal)  
- Eribulin  
- **Etoposide**  
- **Fluorouracil**  
- Floxuridine  
- **Gemcitabine**  
- Interferon alfa >5 to < 10 million IU/m² | - Ixabepilone  
- Methotrexate  
- Mitomycin  
- Mitoxantrone  
- Omacetaxine  
- **Paclitaxel**  
- *nab*-Paclitaxel  
- **Pemetrexed**  
- Pentostatin  
- Pralatrexate  
- Romidepsin  
- Thiotepa  
- Topotecan  
- Ziv-aflibercept  
- Panitumumab |
## Emetogenic Potential of Chemotherapy Agents

<table>
<thead>
<tr>
<th>Level</th>
<th>IV Agent</th>
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</thead>
<tbody>
<tr>
<td><strong>Minimal Emetic Risk</strong></td>
<td>- Alemtuzumab</td>
</tr>
<tr>
<td>(&lt;10% frequency of emesis)</td>
<td>- Asparaginase</td>
</tr>
<tr>
<td></td>
<td>- Bevacizumab</td>
</tr>
<tr>
<td></td>
<td>- Bleomycin</td>
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<tr>
<td></td>
<td>- Bortezomib</td>
</tr>
<tr>
<td></td>
<td>- Cetuximab</td>
</tr>
<tr>
<td></td>
<td>- Cladribine (2-chlorodeoxyadenosine)</td>
</tr>
<tr>
<td></td>
<td>- Cytarabine &lt;100 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- Decitabine</td>
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<td></td>
<td>- Denileukin diftitox</td>
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<tr>
<td></td>
<td>- Dexrazoxane</td>
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<tr>
<td></td>
<td>- Fludarabine</td>
</tr>
<tr>
<td></td>
<td>- Interferon alfa ≤5 million IU/m²</td>
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<tr>
<td></td>
<td>- Ipilimumab</td>
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<tr>
<td></td>
<td>- Methotrexate ≤50 mg/m²</td>
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<td></td>
<td>- Ofatumumab</td>
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<tr>
<td></td>
<td>- Panitumumab</td>
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<td></td>
<td>- Pegasparagase</td>
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<td></td>
<td>- Peginterferon</td>
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<tr>
<td></td>
<td>- Pertuzumab</td>
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<td></td>
<td>- Rituximab</td>
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<td></td>
<td>- Temsirolimus</td>
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<tr>
<td></td>
<td>- Trastuzumab</td>
</tr>
<tr>
<td></td>
<td>- Valrubicin</td>
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<td></td>
<td>- VinBLASTine</td>
</tr>
<tr>
<td></td>
<td>- VinCRIStine</td>
</tr>
<tr>
<td></td>
<td>- VinCRIStine (liposomal)</td>
</tr>
<tr>
<td></td>
<td>- VinORELbine</td>
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</tbody>
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### Emetogenic Potential of Chemotherapy Agents

<table>
<thead>
<tr>
<th>Level</th>
<th>Oral Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to High Emetic Risk; Prophylaxis Recommended</td>
<td>- Altretamine</td>
</tr>
<tr>
<td>= Ondansetron 16-24 mg/day per oral start before chemotherapy and continue</td>
<td>- Busulfan ≥4 mg/day</td>
</tr>
<tr>
<td></td>
<td>- Ceritinib</td>
</tr>
<tr>
<td></td>
<td>- Crizotinib</td>
</tr>
<tr>
<td></td>
<td>- Cyclophosphamide ≥100 mg/m²/day</td>
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<tr>
<td></td>
<td>- Estramustine</td>
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<tr>
<td></td>
<td>- Etoposide</td>
</tr>
<tr>
<td></td>
<td>- Lenvatinib</td>
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<tr>
<td></td>
<td>- Lomustine (single day)</td>
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<td></td>
<td>- Olaparib</td>
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<td></td>
<td>- Mitotane</td>
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<td></td>
<td>- Panobinostat</td>
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<tr>
<td></td>
<td>- Procarbazine</td>
</tr>
<tr>
<td></td>
<td>- Temozolomide &gt;75 mg/m²/day</td>
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<tr>
<td></td>
<td>- Vismodegib</td>
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</tbody>
</table>

## Emetogenic Potential of Chemotherapy Agents

<table>
<thead>
<tr>
<th>Level</th>
<th>Oral Agent</th>
</tr>
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<tbody>
<tr>
<td>Minimal to Low Emetic Risk; As Needed</td>
<td>- Bexarotene</td>
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<tr>
<td></td>
<td>- Busulfan &lt;4 mg/day</td>
</tr>
<tr>
<td></td>
<td>- Cabozantinib/Vandetanib</td>
</tr>
<tr>
<td></td>
<td>- Capecitabine</td>
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<tr>
<td></td>
<td>- Chlorambucil</td>
</tr>
<tr>
<td></td>
<td>- Cyclophosphamide &lt;100 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>- Dabrafenib/Trametinib/</td>
</tr>
<tr>
<td></td>
<td>- Vemurafenib</td>
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<tr>
<td></td>
<td>- Erlotinib/Gefitinib/Afatinib</td>
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<tr>
<td></td>
<td>- Everolimus</td>
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<tr>
<td></td>
<td>- Fludarabine</td>
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<tr>
<td></td>
<td>- Hydroxyurea</td>
</tr>
<tr>
<td></td>
<td>- Ibrutinib</td>
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<td></td>
<td>- Idelalisib</td>
</tr>
<tr>
<td></td>
<td>- Imatinib/Nilotinib/Dasatinib/Bosutinib/Ponatinib</td>
</tr>
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<td>- Lapatinib/Palbociclib</td>
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<td></td>
<td>- Melphalan</td>
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<td></td>
<td>- Mercaptopurine/Thioguanine</td>
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<tr>
<td></td>
<td>- Methotrexate</td>
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<tr>
<td></td>
<td>- Pazopanib/Sunitinib/Axitinib/Sorafenib</td>
</tr>
<tr>
<td></td>
<td>- Regorafenib</td>
</tr>
<tr>
<td></td>
<td>- Ruxolitinib</td>
</tr>
<tr>
<td></td>
<td>- Temozolomide ≤75 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>- Thalidomide/Lenalidomide/Pomalidomide</td>
</tr>
<tr>
<td></td>
<td>- Topotecan</td>
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<tr>
<td></td>
<td>- Tretinoin</td>
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<tr>
<td></td>
<td>- Vorinostat</td>
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## Antiemetics: ASCO Clinical Practice Guideline Update for CINV

<table>
<thead>
<tr>
<th>Emetogenic Category</th>
<th>Acute</th>
<th>Followed by</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5-HT₃ + NK₁ antagonist/ Olanzapine + Dexamethasone</td>
<td>NK₁ antagonist day 2 and 3 (if Aprepitant day 1) / Olanzapine day 2 -4 + Dexamethasone days 2-4</td>
<td>Dexamethasone days 2-4</td>
</tr>
<tr>
<td></td>
<td>Netupitant 300 mg + Palonosetron 0.5 mg tab PO (Akynzeo®) + Dexamethasone</td>
<td>Dexamethasone days 2-4</td>
<td>Dexamethasone days 2-4</td>
</tr>
<tr>
<td>Moderate</td>
<td>5-HT₃ + Dexamethasone ± NK₁ antagonist/ Olanzapine</td>
<td>Single-agent Dexamethasone days 2 and 3 ± NK₁ antagonist/ Olanzapine</td>
<td>No preventive measures</td>
</tr>
<tr>
<td>Low</td>
<td>Dexamethasone or Metoclopramide or Prochorperazine or 5HT₃</td>
<td>No preventive measures</td>
<td>No preventive measures</td>
</tr>
<tr>
<td>Minimal</td>
<td>No preventive measures</td>
<td>No preventive measures</td>
<td>No preventive measures</td>
</tr>
</tbody>
</table>

**NK₁**: Aprepitant 125 mg oral or Fosaprepitant 150 mg IV single dose
### Estimating Nutritional Needs

<table>
<thead>
<tr>
<th>Nutrient/Measurement</th>
<th>Estimated Need</th>
<th>Additional Considerations</th>
</tr>
</thead>
</table>
| Calories (kcal/kg BW)* | 20-35 kcals/kg for adults  
Indirect calorimetry provides a more accurate measurement of resting energy expenditure | - Calculations are used as a starting point taking into consideration age, body composition, physical activity, medical issues, stress factors, and individual differences |
| Protein (g/kg BW) | 0.8 g protein/kg for healthy adults  
↑ needs up to 1.5-2.0 g/kg to support anabolism during oncology treatment | - Patients undergoing cancer treatment can have increased protein requirements in the presence of wounds, enterocutaneous fistulas, high-volume diarrhea, loss from drains or leaks  
- Nitrogen balance study can be the most accurate measurement of protein requirements |
## Estimating Nutritional Needs

<table>
<thead>
<tr>
<th>Nutrient/Measurement</th>
<th>Estimated Need</th>
<th>Additional Considerations</th>
</tr>
</thead>
</table>
| Fluid (mL/kg BW)     | 25-40 mL/kg    | - Dependent on age, renal function, urine output, losses from vomiting, diarrhea, drains, and physical activity  
|                      |                | - Replacement of fluid may be needed during cancer treatment |
### RINV: Emetic Risk Categories of Radiation

<table>
<thead>
<tr>
<th>Emetic Risk</th>
<th>Irradiated area</th>
<th>Antiemetic guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt; 90%)</td>
<td>Total Body (TBI)</td>
<td>Prophylaxis with 5-HT3 receptor antagonist + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Total Nodal Irradiation</td>
<td></td>
</tr>
<tr>
<td>Moderate (60-90%)</td>
<td>Upper Abdomen</td>
<td>Prophylaxis with 5-HT3 receptor antagonist + Optional Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Upper Body Irradiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Half Body Irradiation</td>
<td></td>
</tr>
<tr>
<td>Low (30-60%)</td>
<td>Lower Thorax and Pelvis Cranium, Craniospinal, and Head &amp; Neck</td>
<td>Prophylaxis or Rescue with 5-HT3 receptor antagonist</td>
</tr>
<tr>
<td>Minimal (&lt; 30%)</td>
<td>Extremities Breast</td>
<td>Rescue with Dopamine Receptor antagonist or 5-HT3 receptor antagonist</td>
</tr>
</tbody>
</table>
• **5-HT\textsubscript{3} Antagonists**
  - Ondansetron (Zofran\textsuperscript{®}, Onsia\textsuperscript{®})
  - Granisetron (Kytril\textsuperscript{®})
  - Ramosetron (Nasea\textsuperscript{®})
  - Palonosetron (Aloxi\textsuperscript{®})

• **NK\textsubscript{1} Receptor Antagonists**
  - Aprepitant (Emend\textsuperscript{®})
  - Fosaprepitant (Ivemend\textsuperscript{®})

• **Corticosteroids**
  - Dexamethasone
  - Methylprednisolone

• **Antipsychotics**
  - Haloperidol
    - *Olanzapine (Zyprexa\textsuperscript{®})*
  - Prochlorperazine (Stemetil\textsuperscript{®})

• **Other agents**
  - Metoclopramide
  - Benzodiazepines
  - Antihistamines
  - Cannabinoids
Chemotherapy Associated Mucositis
Risk of chemotherapy-induced stomatitis

- **Younger patients** have a relatively greater risk of chemotherapy-induced stomatitis, perhaps related to a higher epithelial mitotic rate
- Nutritional status
- Type of malignancy
- The quality of oral care during treatment
- Pretreatment neutrophil counts
- The use of hematopoietic growth factor support during therapy
# Mucositis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy for head and neck cancer</td>
<td>85–100</td>
<td>25–45</td>
</tr>
<tr>
<td>Stem-cell transplantation</td>
<td>75–100</td>
<td>25–60</td>
</tr>
<tr>
<td>Solid tumors with myelosuppression</td>
<td>5–40</td>
<td>5–15</td>
</tr>
</tbody>
</table>

J Support Oncol 2007;5(suppl 1):013–021
Mechanism of interleukin-33 (IL-33)-mediated CPT-11-induced intestinal mucositis and potential therapeutic targets.
Pathobiology of Mucositis

Normal epithelium

Phase I
Initiation

Phase II/III
Messaging, signaling, and amplification

Phase IV
Ulceration (mucositis)

Phase V
Healing

Radiation

Basal cell
Chemotherapy
Blood vessel
Inflammatory cell
Fibroblast

Bacteria

CELLULAR MEDIATORS OF MUCOSITIS

Chemotherapy or Radiotherapy

Nuclear factor kappa B (NF-kB)

- TNF-α
- Mitogen-activated protein kinases (MAPK)
- COX-2
- IL-1β
- Tyrosine kinase
- Matrix metalloproteinase (MMP)

1, 3
Chemotherapy Agents Associated with Mucosal Toxicity

| Actinomycin D | Cytarabine | Imatinib (16%) | Paclitaxel (3%) |
| Afatinib (72%) | Docetaxel (13%) | Interferon | Palbociclib (25%) |
| Alemtuzumab | Doxorubicin | Irinotecan | Pazopanib (4%) |
| Bleomycin | Epirubicin | Ixabepilone (29%) | Pazopanib (4%) |
| Bortezomib | Erlotinib (17%) | Lapatinib (15%) | Pazopanib (4%) |
| Busulfan (high doses) | Everolimus (44%) | Lenvatinib (41%) | Procarbazine |
| Capecitabine | Etoposide | Melphalan (high doses) | Regorafenib (33-40%) |
| Carboplatin | Fludarabine | 6-MP | Rituximab |
| Cetuximab (10-20%) | Fluorouracil | Methotrexate | Sorafenib (28%) |
| Chlorambucil | Gefitinib | Mitomycin | Sunitinib (38%) |
| Cisplatin | Gemcitabine | Mitoxantrone | Temsirolimus (41%) |
| Cyclophosphamide | Hydroxyurea | Oxaliplatin | Thiotepa |
| | Idoxofur | Ifosfamide | Topotecan |
| | Ifosfamide | Ifosfamide | Trastuzumab |

Risk of Oral Mucositis according to type of anticancer treatment

- Navelbine
- Gemcitabine
- Doxorubicin
- Docetaxel
- Paclitaxel
- 5-FU
- Cisplatin
- MTX
- Cyclophosphamide
- HD-CT (BMT)
- HD-RT (HNC)
- Standard chemotherapy

Relative risk of developing oral mucositis

- Low
- 20%
- 40%
- 60%
- 80%
- 100%
Clinical differences in onset, severity, and resolution of chemotherapy- and radiation-induced oral mucositis.
Toxicity grading of oral mucositis according to WHO and NCI-CTCAE

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Grade 0 (None)</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (life threatening)</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>None</td>
<td>Oral soreness, Erythema</td>
<td>Oral erythema, ulcers, can eat solids</td>
<td>Oral ulcers, requires liquid diet only</td>
<td>Oral alimentation not possible</td>
<td>-</td>
</tr>
<tr>
<td>Oral Mucositis (Stomatitis)</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
<td>Severe pain; interfering with oral intake</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0</td>
<td>-</td>
<td>Painless ulcers, erythema, or mild soreness in the absence of lesions</td>
<td>Painful erythema, edema, or ulcers, but can eat or swallow</td>
<td>Painful erythema, edema, or ulcers requiring IV hydration</td>
<td>Severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation</td>
<td>-</td>
</tr>
<tr>
<td>NCI-CTC Chemotherapy-induced stomatitis/pharyngitis (oral/pharyngeal mucositis)</td>
<td>None</td>
<td>Erythema of mucosa</td>
<td>Patchy pseudomembranous reaction (patches generally &lt; or = 1.5 cm in diameter and noncontiguous)</td>
<td>Confluent pseudomembranous reaction (contiguous patches generally &gt; 1.5 cm in diameter)</td>
<td>Necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion</td>
<td>-</td>
</tr>
<tr>
<td>NCI-CTC Mucositis due to radiation</td>
<td>None</td>
<td>Painless ulcers, erythema, or mild soreness in the absence of lesions</td>
<td>Painful erythema, edema, or ulcers, but can eat or swallow</td>
<td>Painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutrition support</td>
<td>Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia</td>
<td>-</td>
</tr>
<tr>
<td>NCI-CTC Stomatitis/Pharyngitis (Oral/Pharyngeal mucositis) for BMT studies</td>
<td>None</td>
<td>Painless ulcers, erythema, or mild soreness in the absence of lesions</td>
<td>Painful erythema, edema, or ulcers, but can eat or swallow</td>
<td>Painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutrition support</td>
<td>Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia</td>
<td>-</td>
</tr>
</tbody>
</table>

CA Cancer J Clin 2001;51:290-315
Mucositis: Clinical manifestations

• The physical symptoms of mucositis begin 5 to 10 days after chemotherapy
• Damage is often bilateral and involves non-keratinized sites, including the buccal and labial mucosa, tongue, soft palate, and floor of the mouth.
## Oral Mucositis Prevention

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryotherapy</strong></td>
<td>30 minutes of oral cryotherapy in patients receiving bolus 5-fluorouracil (5-FU) chemotherapy <em>(Level II, grade A)</em></td>
</tr>
<tr>
<td><strong>Palifermin</strong></td>
<td>Recombinant Human Keratinocyte Growth Factor-1 (KGF-1/palifermin) be used to prevent oral mucositis (at a dose of 60 µg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplant) in patients receiving high dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy <em>(Level of Evidence II)</em>.</td>
</tr>
<tr>
<td><strong>Low-level laser therapy</strong></td>
<td>Low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm²) be used to prevent oral mucositis in patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy, with or without total body irradiation <em>(Level of Evidence II)</em>.</td>
</tr>
</tbody>
</table>

## Oral Mucositis Prevention

<table>
<thead>
<tr>
<th>Pain Control</th>
<th>Patient-controlled analgesia with morphine be used to treat pain due to oral mucositis in patients undergoing hematopoietic stem cell transplantation <em>(Level of Evidence II)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzydamine</td>
<td>Benzydamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy <em>(Level of Evidence I)</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amifostine</td>
<td>Intravenous amifostine be used, at a dose of $\geq 340 \text{ mg/m}^2$, to prevent radiation proctitis in patients receiving radiation therapy (Level of Evidence II)</td>
</tr>
<tr>
<td>Amifostine</td>
<td>Intravenous amifostine be used to prevent esophagitis induced by concomitant chemotherapy and radiation therapy in patients with non-small cell lung carcinoma (Level of Evidence III)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to prevent radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (II).</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Probiotics containing Lactobacillus species be used to prevent diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (III).</td>
</tr>
</tbody>
</table>
Oral Mucositis Treatment

<table>
<thead>
<tr>
<th>Oral care Protocol</th>
<th>Oral care protocols be used to prevent oral mucositis in all age groups and across all cancer treatment modalities (III).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryotherapy</strong></td>
<td>Oral cryotherapy be used to prevent oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT (III).</td>
</tr>
<tr>
<td><strong>Low-level laser therapy</strong></td>
<td>Low-level laser therapy (wavelength around 632.8 nm) be used to prevent oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer (III).</td>
</tr>
<tr>
<td><strong>Transdermal Fentanyl</strong></td>
<td>Transdermal fentanyl may be effective to treat pain due to oral mucositis in patients receiving conventional or high-dose chemotherapy, with or without total body irradiation (III).</td>
</tr>
</tbody>
</table>

## Oral Mucositis Treatment

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine mouthwash</td>
<td>0.2% morphine mouthwash may be effective to treat pain due to oral mucositis in patients receiving chemoradiation for head and neck cancer (III).</td>
</tr>
<tr>
<td>Doxepin mouthwash</td>
<td>0.5% doxepin mouthwash may be effective to treat pain due to oral mucositis (IV).</td>
</tr>
<tr>
<td>Zinc supplements</td>
<td>Systemic zinc supplements administered orally may be of benefit to prevent oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (III).</td>
</tr>
</tbody>
</table>

### GI Mucositis Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>Octreotide, at a dose of ≥100 µg subcutaneously twice daily, be used to treat diarrhea induced by standard- or high-dose chemotherapy associated with hematopoietic stem cell transplantation (HSCT), if loperamide is ineffective (II).</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Sucralfate enemas be used to treat chronic radiation-induced proctitis in patients with rectal bleeding (III).</td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
<td>Hyperbaric oxygen be used to treat radiation-induced proctitis in patients receiving radiation therapy for a solid tumor (IV).</td>
</tr>
</tbody>
</table>

### Oral Mucositis Treatment *not recommend*

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Lozenges</td>
<td>PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste <em>not be used</em> to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (II).</td>
</tr>
<tr>
<td>Antimicrobial mouthwash</td>
<td>Iseganan antimicrobial mouthwash <em>not be used</em> to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II), or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer (II).</td>
</tr>
<tr>
<td>Sucralfate mouthwash</td>
<td>Sucralfate mouthwash <em>not be used to prevent</em> oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for head and neck cancer.</td>
</tr>
</tbody>
</table>

### Oral Mucositis Treatment *not recommend*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucralfate mouthwash</td>
<td>Sucralfate mouthwash <em>not be used to treat</em> oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (II) for head and neck cancer.</td>
</tr>
<tr>
<td>Glutamine IV</td>
<td>Intravenous glutamine <em>not be used to prevent</em> oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).</td>
</tr>
<tr>
<td>Chlorhexidine mouthwash</td>
<td>Chlorhexidine mouthwash <em>not be used to prevent</em> oral mucositis in patients receiving radiation therapy for head and neck cancer (III).</td>
</tr>
<tr>
<td>GM-CSF mouthwash</td>
<td>Granulocyte-macrophage-colony-stimulating factor mouthwash <em>not be used to prevent</em> oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (II).</td>
</tr>
</tbody>
</table>

- [MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014 May 15;120(10):1453-61](#)
Oral Glutamine in Preventing Treatment-Related Mucositis in Adult Patients With Cancer: A Systematic Review

Caitlin Sayles, PharmD\textsuperscript{1,2}; Stephen C. Hickerson, PharmD, MS\textsuperscript{1,2,3}; Radhika R. Bhat, MS\textsuperscript{4}; Jacob Hall, PharmD, BCNSP\textsuperscript{2}; Kevin W. Garey, PharmD, MS\textsuperscript{4}; and Meghna V. Trivedi, PharmD, PhD, BCPP\textsuperscript{1}

Abstract

Background: Breakdown of the mucosal barrier resulting in mucositis is a common adverse event in patients with cancer receiving chemotherapy and/or radiation. Many studies have evaluated the use of oral glutamine to prevent mucositis in these settings, but current guidelines make no recommendations with regard to its use. Our objective was to systematically review the evidence for the use of oral glutamine in preventing mucositis in adult patients with cancer undergoing chemotherapy and/or radiation.

Methods: A systematic search of English-language literature was done via MEDLINE using the search terms glutamine, cancer, and mucositis or esophagitis or stomatitis. Five studies conducted in adult patients with cancer receiving chemotherapy and/or radiation were included in the systematic review. Single-agent oral glutamine with or without added calcium oxide was evaluated. Overall, oral glutamine was shown to be effective in 11 of the 15 studies included in the systematic review. Significant reduction in the incidence of grade 2, 3, or 4 mucositis was achieved with less weight loss as well as the duration, time of onset, and maximum grade of mucositis.

Conclusion: In summary, the favorable efficacy and low toxicity of oral glutamine observed in clinical trials reviewed provide a strong rationale for large randomized placebo-controlled trials to further evaluate its efficacy in preventing mucositis in patients with cancer receiving chemotherapy and/or radiation.

Keywords

Glutamine, mucositis, esophagitis, stomatitis, cancer, chemotherapy, radiation

Mucositis is characterized by painful inflammation and ulceration of the mucosal membranes lining the digestive tract and is a frequent and adverse complication of chemotherapy, radiation therapy, or even targeted anticancer therapy. It severely affects the clinical outcomes and quality of life of patients with cancer.1-4 Adverse outcomes related to mucositis include delays in therapy, reduction in dose intensity, nutrition compromise, and increased risk for infection.4-6 Depending on the type of cancer, treatment modality (chemotherapy vs radiation), types of chemotherapy, and dose intensity, 60%-100% of patients with cancer are affected by this complication.7-9 Treatment delays and dose reductions are common consequences of severe mucositis during anticancer therapy, reported in up to 35% and 60% of patients, respectively.10

The high morbidity associated with mucositis warrants clinical investigation of strategies to prevent this toxicity. Although oral hygiene and cryotherapy are generally recommended to prevent mucositis and reduce its severity, this does not work for all patients as they work best when used with chemotherapy with short half-lives.10,11 Two pharmacological agents are recommended for the prevention of mucositis secondary to cancer therapy by the 2014 Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines.12 The first agent, recombinant human keratinocyte growth factor 1 (KGF-1; palifermin), is recommended in patients with hematological malignancies receiving high-dose chemotherapy and total-body irradiation prior to autologous stem cell transplantation. The second agent, bexarotene, is recommended in patients with head and neck cancer receiving moderate-dose radiation therapy without concurrent chemotherapy. The guideline also suggests that zinc supplements administered orally may be of benefit in the prevention of oral mucositis in patients with oral cancer receiving radiation therapy or chemoradiation.

In the past 2 decades, oral glutamine has been investigated in clinical studies to prevent oral and esophageal mucositis related to chemotherapy and radiation therapy. Based on
**Oral Mucositis Treatment *not recommend***

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misoprostol mouthwash</td>
<td>Misoprostol mouthwash <em>not be used to prevent</em> oral mucositis in patients receiving radiation therapy for head and neck cancer (III).</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Systemic pentoxifylline, administered orally, <em>not be used to prevent</em> oral mucositis in patients undergoing bone marrow transplantation (III).</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Systemic pilocarpine, administered orally, <em>not be used to prevent</em> oral mucositis in patients receiving radiation therapy for head and neck cancer (III), or in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).</td>
</tr>
</tbody>
</table>

GI Mucositis Treatment *not recommend*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucralfate</td>
<td>Systemic sucralfate, administered orally, not be used to treat gastrointestinal mucositis in patients receiving radiation therapy for a solid tumor (I).</td>
</tr>
<tr>
<td>ASA</td>
<td>5-acetyl salicylic acid (ASA), and the related compounds mesalazine and olsalazine, administered orally, not be used to prevent acute radiation-induced diarrhea in patients receiving radiation therapy for a pelvic malignancy (I).</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Misoprostol suppositories not be used to prevent acute radiation-induced proctitis in patients receiving radiation therapy for prostate cancer (I).</td>
</tr>
</tbody>
</table>

Diarrhea

• Chemotherapy-induced
  a. Epithelial cell lining of the GI tract is normally replaced every 3 to 5 days and many chemotherapy agents can damage this lining
  b. Chemotherapy-induced diarrhea is usually considered secretory and is thought to be caused by direct toxicity to the epithelial cells leading to inflammation with prostaglandin release
Diarrhea

• Chemotherapy-induced
  c. Chemotherapy-induced diarrhea may also have an exudative component to it
d. Any chemotherapeutic agent may cause diarrhea, but the worst offenders are fluorouracil, methotrexate, cytarabine, and stem cell transplant conditioning
e. Continuous infusions cause more diarrhea than short IV infusions
Chemotherapy-induced diarrhea (CID)

- is most commonly described with fluoropyrimidines (particularly 5-fluorouracil and capecitabine), irinotecan, pemetrexed, cabazitaxel, bortezomib, vorinostat
- Several molecularly targeted agents: Sorafenib, Sunitinib
- Agents targeting the epidermal growth factor receptor [EGFR]: Lapatinib.
Diarrhea

• Chemotherapy-induced
  f. 50 to 80% of patients receiving modulated fluorouracil regimens, single-agent irinotecan, and combination regimens of irinotecan and fluorouracil experience diarrhea and greater than 30% of these patients may experience grade 3 to 5 diarrhea
g. Diarrhea caused by irinotecan is unique as it has an early onset and a late onset component
Diarrhea

• Chemotherapy-induced
  
i. Early onset diarrhea occurs in the first 24 hours after chemotherapy administration

  (1) Acts as a selective, reversible acetylcholinesterase inhibitor and possibly as an agonist at acetylcholine receptors
  
  (2) Other potential mechanisms are parasympathetic discharge, stimulation of serotonin receptors, and release of thromboxane (TX)-A2

  (3) Patients can experience other cholinergic effects (abdominal cramping, diaphoresis, flushing, hypersalivation, hyperlacrimation, rhinitis, and visual changes) in addition to diarrhea
Diarrhea

• Chemotherapy-induced
  i. Early onset diarrhea occurs in the first 24 hours after chemotherapy administration (Cont.)
    (4) Incidence appears to be dose related
    (5) Estimated > 80% of patients had mild to moderate symptoms and up to 10% experience severe symptoms
    (6) Symptom onset usually begins during the irinotecan infusion
Diarrhea

• Chemotherapy-induced

  ii. Late occurs > 24 hours after chemotherapy
      (1) Estimated to occur in 60% to 87% of patients
      (2) Median time to onset is 5 days after the Q21D regimen and 11 days after the weekly regimen
      (3) Mechanism is unknown but may be due to direct damage to intestinal mucosa by SN-38, which is a metabolite of irinotecan
      (4) Appears to be dose related
Constipation can be defined as a decreased frequency of defecation (usually less than three bowel movements per week) accompanied by discomfort or difficulty.

It is a common problem in patients with cancer, usually being due to a combination of poor oral intake and drugs, such as opioid analgesics or antiemetic agents, that slow intestinal transit time. As an example, 5HT3 receptors are present on enteric neurons, and ondansetron was shown to slow colonic transit time in healthy subjects.
• In a randomized study, subcutaneous methylnaltrexone administration showed excellent efficacy and did not affect central analgesia or precipitate opioid withdrawal.

• FDA approval in 2008 for the management of opioid-induced constipation in patients with advanced illness who are receiving palliative care. Its use in other settings, such as medication-induced constipation, has not been carefully investigated yet. (See "Cancer pain management with opioids: Prevention and management of side effects", section on 'Bowel issues'.)
• **Vinca alkaloids** — Constipation is rarely a dose-limiting toxicity for chemotherapeutic agents except for the vinca alkaloids (eg, vincristine, vinblastine, and vinorelbine), especially vincristine.

• These drugs have pronounced neuropathic effects and increase GI transit time.

• The constipating effect of vinca alkaloid therapy is usually apparent after the first dose and is typically not cumulative. It is most prominent three to ten days after chemotherapy and then resolves in most cases after a few days.
CONSTIPATION

- Constipation occurs in one-quarter to one-third of patients and is severe in 2 to 3 percent
  - In one series of 392 patients, 2.8 percent required hospitalization for adynamic ileus.

- Vincristine-induced constipation is more severe at higher doses (above 2 mg).
  - This was illustrated in a report of 104 patients with Hodgkin's or non-Hodgkin lymphoma.
  - Vincristine was given in a noncapped dose of 1.4 mg/m², and 90 percent of patients received more than 2 mg in the first dose. Severe constipation occurred in 10 percent. Rapid improvement usually occurred within a few weeks after the cessation of therapy.
• Constipation is also more frequent and may be more severe (presenting as a bowel obstruction or paralytic ileus) in patients treated with the liposome-encapsulated version of vincristine (Marqibo®), which is approved only for treatment of refractory adult acute lymphoblastic leukemia.
• **Thalidomide and analogs** — Thalidomide and its analogs lenalidomide and pomalidomide have shown promise for the treatment of refractory multiple myeloma and other disorders.
  - The most common toxicity with thalidomide, beside sedation, is constipation. In a major myeloma trial, constipation developed in 35 percent of patients at 200 mg/day and in 59 percent at 800 mg/day.
  - These rates seem higher than those observed in a phase II trial of thalidomide (starting dose 800 mg daily) in patients with recurrent high-grade glioma, in which constipation was the most common toxicity, but only occurred in 19 percent of patients; no severe episodes were noted.
• In clinical trials, pomalidomide has been associated with diarrhea or constipation in about one-third of treated patients, none of which were severe.

• Vandetanib — Vandetanib is a multitargeted inhibitor of several tyrosine kinases. In clinical trials involving patients with medullary thyroid cancer and lung cancer, vandetanib was associated with constipation in 9 to 37 percent of patients, with 0 to 3 percent severe. Vandetanib is more often associated with diarrhea.
• Belinostat — Belinostat is a histone deacetylase inhibitor that is approved for treatment of peripheral T-cell lymphoma. In an initial clinical trial involving 129 patients, belinostat was associated with constipation in 23 percent of patients, 2 percent severe. Diarrhea was equally common.
CONSTIPATION: Treatment

- The treatment of chemotherapy-induced constipation begins with anticipation and prevention.
- Laxatives should be started at the first sign of constipation or should be given routinely to prevent constipation.
- The most frequently used laxatives
  - **Docusate**: Not effective alone for opioid or vinca alkaloid constipation, Effect in 1-3 days
  - **Senna**: Effect in 6 to 12 hours, Very effective in preventing vinca- and opioid-induced constipation, Titrate dose to desired effect, usually one bowel movement every 48 hours

**CONSTIPATION: Treatment**

- The most frequently used laxatives (Cont.)
  - Bisacodyl: Best when used for acute treatment or disimpaction

- If these agents are not effective,
  - **Magnesium salts:** Effective in 6 to 8 hours, Caution in patients with CHF and renal insufficiency
  - **Polyethylene Glycol- Electrolyte Solution (Miralax®):** Very effective agent; effect seen in 2 to 4 days
  - **Lactulose:** Very effective agent; effect seen in 1 to 2 days, Sweet taste can be an issue, Caution in diabetics
  - **Sorbitol:** Very effective agent; effect seen in 1 to 2 days, Sweet taste can be an issue, Good choice in patients with renal impairment
Cancer–related anorexia/cachexia syndrome (CACS)

- Weight loss of greater than 5% premorbid weight predicted a poorer prognosis
- Cachexia is the main cause of death in 20% of cancer patients
- Weight loss in cancer patients involves both fat and lean muscle mass
Etiologies of Involuntary Weight Loss

1. Chronic nausea secondary to autonomic dysfunction leading to decreased gastric and intestinal motility, constipation, depression or medications, such as opioid therapy
2. Anorexia
3. Metabolic abnormalities including decreased skeletal muscle proteins, increased metabolic abnormalities or profound lipolysis
Etiologies of Involuntary Weight Loss

4. Changes in taste and smell due to chemotherapy or radiation therapy

a. Chemotherapy agents associated with taste and smell alterations include carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, fluorouracil, methotrexate, paclitaxel, and tegafur

b. Chemotherapy can lead to olfactory and gustatory receptor destruction

c. Initial infusion of various antiproliferative chemotherapy agents can result in an immediate bitter taste, in addition to taste alterations that can continue for months - may be due to drug being released into saliva
The Importance of Myosin in Cachexia
Anorexia Cachexia Syndrome in Cancer

NPY = NeuroPeptide Y
CRF = Corticotropin-Releasing Factor
CNTF = Ciliary NeuroTropic Factor
The potential modalities of pharmacological intervention of cancer anorexia-cachexia syndrome

- **Glucocorticoids**
  - Progesterones (Megace)
  - NSAIDs
  - Cyproheptadine
  - BCAA
  - Metoclopramide

- **Appetite stimulants with or without antinausea effect**

- **Metoclopramide**
  - Gastroprokinetic agents with or without antinausea effect

- **Glucocorticoids**
  - Progesterones (Megace)
  - Eicosapentanoic acid
  - Melatonin
  - Thalidomide
  - NSAIDs
  - Pentoxifylline

- **Inhibitors of production/release of cytokines and other factors**

- **BCAA**
  - Eicosapentanoic acid
  - B-Adrenoceptor agonist (Formoterol)
  - Anabolic steroids (Decadurabolin 50 mg inj.)

- **Eicosapentanoic acid**
  - Blockers of fat and muscle tissue wasting

- **The potential modalities of pharmacological intervention of cancer anorexia-cachexia syndrome**

- **Hypothalamus**
  - Higher Cortical Center
  - Limbic Lobe
  - Cytokine Neuropeptide Amine Prostanoitd

- **Blood-Brain Barrier**
  - Stomach
  - Liver
  - Fat
  - Muscle

- **Cancer**
  - Cytokine Peptide PIP LNF Prostanoitd

- **Formoterol**
  - Adrenoceptor agonist

- **Decadurabolin 50 mg inj.**
  - Anabolic steroids

- **Blockers of fat and muscle tissue wasting**
## Adverse Effects of Treatment in Head and Neck and Gastric Cancers

<table>
<thead>
<tr>
<th>Nutritional Adverse Effects</th>
<th>Causal Treatment Modality</th>
<th>Nutrition Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia/odynophagia</td>
<td>Chemotherapy Radiation</td>
<td>- Initiate texture-modified diet</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td>- Obtain a swallow evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Place feeding tube for nutrition</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Chemotherapy Radiation</td>
<td>- Initiate small, frequent low-fat meals</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td>- Initiate antiemetics</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>- Place feeding tube for nutrition</td>
</tr>
<tr>
<td>Loss of appetite and early satiety</td>
<td>Chemotherapy Radiation</td>
<td>- Initiate small, frequent meals</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td>- Modify menu to preference</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>- Initiate an appetite stimulant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Place feeding tube for nutrition</td>
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</tbody>
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# Adverse Effects of Treatment in Head and Neck and Gastric Cancers

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| Taste changes               | Chemotherapy, Radiation, Surgery | - Modify menu to preference and tolerance  
                              |                           | - Initiate probiotics  
                              |                           | - Initiate mouth rinse     |
| Mouth sores                 | Chemotherapy              | - Initiate texture modification  
                              |                           | - Initiate mouth rinse  
                              |                           | - Institute pain management protocol  
                              |                           | - Modify menu to tolerance     |
| Diarrhea                    | Chemotherapy, Radiation   | - Initiate a low-fiber and residue diet and/or tube-feeding regimen  
                              |                           | - Institute antidiarrheal medication  
                              |                           | - Increase fluids and zinc supplementation  
                              |                           | - Institute probiotics         |
## Adverse Effects of Treatment in Head and Neck and Gastric Cancers

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| Constipation                | Chemotherapy             | - Institute a fiber-containing diet, as swallowing ability allows, and/or tube-feeding regimen with fiber  
                              | Radiation              | - Institute laxatives, stool softeners, and bulk agents (methylcellulose, psyllium)  
                              | Surgery                | - Increase fluids        |
| Renal insufficiency         | Chemotherapy             | - Adjust protein goals as appropriate  
                              |                         | - Monitor electrolytes and restrict or replace as needed |
| Hypomagnesemia              | Chemotherapy             | - Replace magnesium orally or intravenously with medication  
<pre><code>                          |                         | - Initiate high-magnesium diet |
</code></pre>
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</tr>
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</table>
| Fatigue                    | Chemotherapy, Radiation, Surgery | - Increased fluids
                             |                                          | - Evaluate adequacy of calories and protein |
Thank you for your attention