Managing Adverse Events in the Cancer Patient

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Learning Objectives

• Describe the etiology and severity grading of nausea/vomiting, diarrhea and hand-foot syndrome in patients receiving cancer treatment
• Identify potential causes and risk factors of these adverse events
• Appropriately manage these adverse events

Chemotherapy-Induced Nausea/Vomiting

• Ranked by patients as one of the most feared adverse events of cancer treatment
• Complications include
  – Decreased QOL, performance status
  – Electrolyte disturbances, dehydration
  – Weight loss
  – Esophageal tears
  – Anxiety
  – Higher healthcare resource utilization
• If uncontrolled can compromise adherence and treatment outcomes

References

5 Types of CINV

- Acute
  - Occurs within 24 hrs of chemo, onset usually 1-2 hrs
- Delayed
  - Occurs ≥ 24 hrs after chemo, peaks at 48-72 hrs
- Breakthrough
  - Occurs despite preventative therapy
- Refractory
  - Occurs despite appropriate preventative and breakthrough therapy
- Anticipatory
  - Learned or conditioned response, occurs before acute CINV symptoms are expected

CINV

- Multiple causes in oncology population
  - Chemotherapy
  - Radiation
  - GI surgeries
  - Disease-related
  - Effect of other medications
- Complex pathology involving multiple neurotransmitters
  - Serotonin (acute, refractory)
  - Dopamine (acute, refractory)
  - Substance P (delayed)
  - Prostaglandins
  - Acetylcholine, histamine, opiate, cannabinoids

Antiemetic Agents

- 5-HT3 receptor antagonists*
  - Dolasetron, granisetron, ondansetron, palonosetron, ramosetron, tropisetron
- NK-1 receptor antagonists*
  - Aprepitant, fosaprepitant
- Corticosteroids*
  - Dexamethasone
- Atypical antipsychotic
  - Olanzapine
- Benzodiazepines
  - Lorazepam
- Phenthoiazinones
  - Prochlorperazine, promethazine
- Butyrophenones
  - Haloperidol
- Benzamide analogs
  - Metoclopramide
- Cannabinoids
  - Dronabinol
- Anticholinergics
  - Scopolamine patch
Drug Specific Risk Factors

- New classification schema in 2005 based on proportion of patients who experience emesis in the absence of effective anti-emetic prophylaxis:
  - High risk (> 90%)
  - Moderate risk (30-90%)
  - Low risk (10-30%)
  - Minimal risk (<10%)

Management of CINV

- Highly emetic
  - NK1 receptor antagonist on Day 1-3 (Day 1 for fosaprepitant)
  - 5-HT3 receptor antagonist on Day 1
  - Corticosteroid on Days 1-3 (or 4)
  - Breakthrough agent
- Moderately emetic
  - 5-HT3 receptor antagonist (palonosetron preferred) on Day 1
  - Corticosteroid on Days 1-3
  - Breakthrough agent
Management of CINV

- Low emetic risk
  - Corticosteroid (dexamethasone 8mg on Day 1)
  - Breakthrough agent
- Minimal emetic risk
  - Breakthrough agent only

Management of CINV

- Prophylaxis is key
  - Administered 30-60 minutes prior to chemotherapy
  - Regimens tailored to level of emetogenic risk
  - Account for risk of delayed N/V (3-5 days out)
  - Should be taken scheduled, not PRN

Management of Breakthrough CINV

- PRN agent available for breakthrough
  - Different mechanism of action
- If effective, schedule that agent
- If refractory, additional agent
  - Escalate prophylactic regimen prior to next dose of chemotherapy regimen
- Administer appropriate hydration, supportive measures
Managing CINV with Oral Chemotherapy

- Managed according to emetic risk
  - High-moderate
    - 5-HT3 receptor antagonist daily
    - Breakthrough agent
  - Low-minimal
    - Breakthrough agent only
    - If CINV, schedule dopaminergic agent

Treatment of Anticipatory CINV

- Prevention is key
- Benzodiazepine
  - Lorazepam or alprazolam night before and morning of treatment
- Behavioral techniques
  - Acupuncture
  - Hypnosis
  - Relaxation techniques
  - Music therapy

Olanzapine for CINV

- 251 patients receiving highly emetogenic chemotherapy
- Olanzapine + palonosetron + dexamethasone (n=121)
- Aprepitant + palonosetron + dexamethasone (n=120)

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Aprepitant</th>
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</thead>
<tbody>
<tr>
<td>CR (acute)</td>
<td>97%</td>
<td>87%</td>
</tr>
<tr>
<td>CR (overall)</td>
<td>77%</td>
<td>73%</td>
</tr>
<tr>
<td>Emesis (overall)</td>
<td>28</td>
<td>16</td>
</tr>
</tbody>
</table>

p=NS

Diarrhea in the Cancer Patient

- Disease related
  - Pancreatic enzyme insufficiency
  - Neuroendocrine tumors
- Infectious
- Dietary
  - Lactose
- Other Medications

- Treatment related
  - Surgical procedures (e.g. bowel resection)
  - Chemotherapy
    - Incidence up to 82%
    - Cytotoxic chemotherapy
    - Oral targeted agents
    - Immunotherapy (ipilimumab)
  - Radiation

Diarrhea

- Mild/Moderate
  - Grade 1: increase of <4 stools/day or mild increase in ostomy output
  - Grade 2: increase of 4-6 stools/day or nocturnal stools or moderate increase in ostomy output
- Severe
  - Grade 3: increase of 7+ stools/day or incontinence or severe increase in ostomy output limiting self-care ADL; require IV hydration
  - Grade 4: Life-threatening consequences requiring urgent intervention

Diarrhea Management

- Grade 1/2, no complicating symptoms
  - Supportive management
    - BRAT die
    - Oral hydration
  - Identify and manage potential causes
    - If non-infectious, initiate pharmacologic therapy
      - Loperamide 4mg at first diarrhea, then 2mg every 2-4h until controlled x12 hours (max 24mg/day)
    - If uncontrolled after 24-48h, additional work-up
      - Consider additional agent
        - Diphenoxylate/atropine
        - Opioids
        - Octreotide 100-150mcg SQ TID
Diarrhea Management

- Grade 3/4 or grade 2 with complicating symptoms
  - Intravenous fluid and electrolyte support
  - Obtain stool sample, administer empiric antibiotics as needed
  - Initiate pharmacologic treatment
  - Administer octreotide if uncontrolled on loperamide or if complicating s/s are present

Palmar Plantar Erythrodysesthesia

- “Hand Foot Syndrome”
- Reported in 6-62% of patients treated with certain chemotherapy drugs/regimens
  - Capecitabine, infusional fluorouracil
  - Doxorubicin
  - Cytarabine
  - Cyclophosphamide
  - Vinorelbine
  - Docetaxel
  - Sorafenib, sunitinib

Grading of Hand Foot Syndrome (HFS)

- Initial presentation: redness, swelling, tingling, discomfort
- Progress to pain, swelling, desquamation, ulceration, blistering, skin breakdown, secondary infection
- Grade 1
  - Minimal skin changes or dermatitis without pain
- Grade 2
  - Skin changes with pain limiting instrumental ADL
- Grade 3
  - Severe skin changes with pain limiting self-care ADL
Prevention and Management

- Moisture
  - Apply thick creams to hands and feet twice daily
- Minimize irritation
  - Avoid products with perfumes, dyes, alcohol
  - Avoid hot water
- Minimize friction
  - Comfortable-fitting shoes with socks
- Cool compresses
- Consider dose-reduction or treatment interruption per product labeling

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Pyridoxine

360 patients initiating treatment with capecitabine

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<thead>
<tr>
<th>Pyridoxine</th>
<th>Placebo</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Overall HFS</td>
<td>140 (77.8%)</td>
<td>147 (81.7%)</td>
</tr>
<tr>
<td>Grade 2/3</td>
<td>57 (31.7%)</td>
<td>55 (30.6%)</td>
</tr>
<tr>
<td>Median cumulative capecitabine dose until HFS</td>
<td>70,000mg/m2 (60,010.9-79,865.1)</td>
<td>70,000mg/m2 (69,384.8-70,615.2)</td>
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Urea-Based Cream

868 patients initiating treatment with sorafenib

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<tr>
<th>Urea-based cream</th>
<th>BSC</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Overall HFS</td>
<td>246 (56%)</td>
<td>316 (73.6%)</td>
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<tr>
<td>Grade ≥2</td>
<td>96 (21.9%)</td>
<td>126 (29.2%)</td>
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<tr>
<td>Median time to first HFS event (days)</td>
<td>84 (45-93)</td>
<td>34 (29-43)</td>
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Summary

• Prophylaxis is key for managing CINV
  – Tailored to patient’s emetic risk
  – Breakthrough medication available
• Diarrhea may be multifactorial
  – Early management is key
• HFS may occur frequently with certain chemotherapy agents
  – Prevention and early management is crucial