Managing Adverse Events in the Cancer Patient

Lisa A Thompson, PharmD, BCOP
Assistant Professor
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

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

Passik et al. J Pain Sympt Manag 2001. 21(2):113-120
Basch et al. J Clin Oncol 2011. 29(31):4189-4198

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

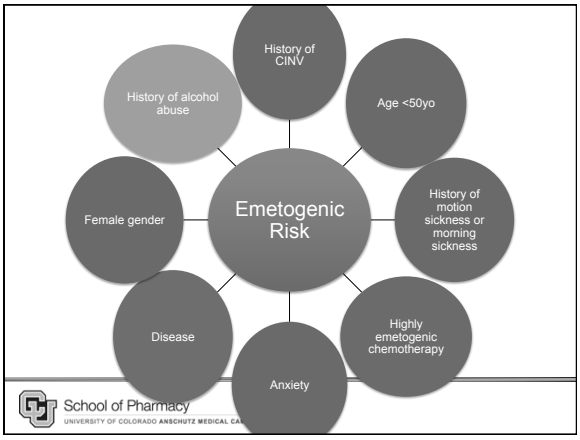
CINV

- 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

Passik et al. J Pain Sympt Manag 2001. 21(2):113-120
Basch et al. J Clin Oncol 2011. 29(31):4189-4198
Am J Health-Syst Pharm. 1999; 729-64

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
- Phenothiazines
  - 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%)

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Basch et al. J Clin Oncol 2011. 29(31):4189-4198

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

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Basch et al. J Clin Oncol 2011. 29(31):4189-4198
NCCN Clinical Practice Guidelines in Oncology
Antiemesis version 1.2012 nccn.org

Management of CINV

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

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Basch et al. J Clin Oncol 2011. 29(31):4189-4198
NCCN Clinical Practice Guidelines in Oncology
Antiemesis version 1.2012 nccn.org

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

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Basch et al. J Clin Oncol 2011. 29(31):4189-4198

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

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Basch et al. J Clin Oncol 2011. 29(31):4189-4198

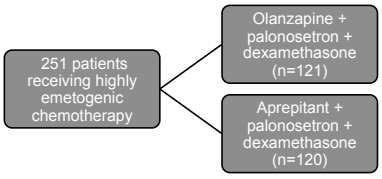
Managing CINV with Oral Chemotherapy

- 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
- Behavorial techniques
  - Acupuncture
  - Hypnosis
  - Relaxation techniques
  - Music therapy

Olanzapine for CINV



	Olanzapine	Aprepitant	
CR (acute)	97%	87%	p=NS
CR (overall)	77%	73%	p=NS
Emesis (overall)	28	16	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

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Benson et al. J Clin Oncol 2004. 22(14):2918-2926
Maroun et al. Curr Oncol 2007. 14(1):13-20

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

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

CTCAE v4.03: June 14, 2010
US Dept of Health and Human Services.

Diarrhea Management

- Grade 1/2, no complicating symptoms
  - Supportive management
    - *BRAT diet*
    - *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

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Benson et al. J Clin Oncol 2004. 22(14):2918-2926

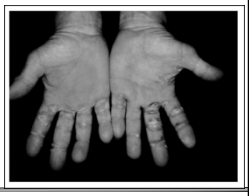
Diarrhea Management

- 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

Benson et al. J Clin Oncol 2004. 22(14):2918-2926

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



Kang et al. J Clin Oncol 2010. 28(24):3824-3829
Kloos et al. J Clin Oncol 2009. 27(10):1675-1684

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

CTCAE v4.03: June 14, 2010
US Dept of Health and Human Services.

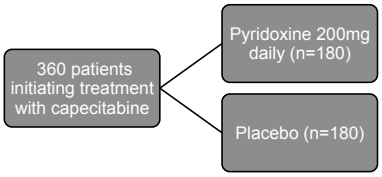
Prevention and Management

- 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

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Kang et al. J Clin Oncol 2010. 28(24):3824-3829

Pyridoxine

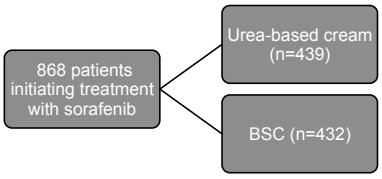


	Pyridoxine	Placebo	
Overall HFS	140 (77.8%)	147 (81.7%)	p=NS
Grade 2/3	57 (31.7%)	55 (30.6%)	p=NS
Median cumulative capecitabine dose until HFS	70,000mg/m2 (60,010.9-79,989.1)	70,000mg/m2 (69,384.8-70,615.2)	p=0.NS

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Kang et al. J Clin Oncol 2010. 28(24):3824-3829

Urea-Based Cream



	Urea-based cream	BSC	
Overall HFS	246 (56%)	318 (73.6%)	p<0.0001
Grade ≥2	96 (21.9%)	126 (29.2%)	p=0.1638
Median time to first HFS event (days)	84 (45-93)	34 (29-43)	p<0.001

School of Pharmacy
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Ren et al. J Clin Oncol 2012. 30(suppl; abstr 4008)

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