Applying the Principles of Antiemetic Therapy to the Management of CINV: A Case-study Approach
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Program Agenda

6:15 a.m. – 6:45 a.m.  Registration and Breakfast Buffet

6:45 a.m. – 6:50 a.m.  Introductory Remarks
  Rowena N. Schwartz, Pharm.D., BCOP, Program Moderator

6:50 a.m. – 7:15 a.m.  Expensive New Antiemetics for Cancer Patients: Where Do They Belong in Therapy?
  Val R. Adams, Pharm.D., FCCP, BCOP

7:15 a.m. – 7:40 a.m.  Case Studies: Management of CINV in the Patient with Cancer
  Rowena N. Schwartz, Pharm.D., BCOP
  Val R. Adams, Pharm.D., FCCP, BCOP

7:40 a.m. – 7:45 a.m.  Question and Answer Discussion

Program Faculty

Rowena N. Schwartz, Pharm.D., BCOP, Program Moderator
Associate Professor, Pharmacy and Therapeutics
School of Pharmacy
University of Pittsburgh
Pittsburgh, Pennsylvania

Val R. Adams, Pharm.D., FCCP, BCOP
Associate Professor, Pharmacy Practice and Science
College of Pharmacy
University of Kentucky
Lucille P. Markey Cancer Center
Lexington, Kentucky
Applying the Principles of Antiemetic Therapy to the Management of CINV: A Case-study Approach

Program Description

Chemotherapy-induced nausea and vomiting (CINV) is a common and dreaded side effect of cancer chemotherapy that adversely affects quality of life and may deter patients from completing the recommended chemotherapy. Despite the development of increasingly effective antiemetic therapies and the availability of authoritative guidelines for their use, the prevalence and impact of CINV remains a concern. Risk factors for CINV include the emetogenic potential of the specific chemotherapeutic agent and individual patient characteristics. Patients receiving multi-day chemotherapy regimens are at risk for both acute CINV (that which occurs within several hours after chemotherapy administration and resolves within 24 hours) and delayed CINV (that which begins more than 24 hours after chemotherapy administration and lasts for days). In addition, recent research concerning the pathophysiology of acute versus delayed CINV underscores the need for a different approach to the treatment of each condition and evidence demonstrating that delayed CINV is more prevalent than previously thought requires increased vigilance on the part of health-care practitioners.

This program will explore considerations in selecting among the available antiemetic agents, including the type, dose, and schedule of chemotherapy (i.e., emetogenic potential); type of CINV (i.e., acute vs. delayed); outcome of previous antiemetic therapy; anticipated adverse effects; the frequency and severity of CINV; and patient characteristics and preference.

Learning Objectives

At the conclusion of this program, participants should be able to:

- Identify the neurotransmitters and explain the pathophysiologic mechanisms involved in CINV.
- Explain the mechanisms of action of the various antiemetic agents used to manage acute and delayed CINV.
- Discuss the basic principles of antiemetic therapy to prevent and treat acute, delayed, anticipatory, breakthrough, and refractory CINV as they apply to specific patient cases.
- Recommend antiemetic therapy for a specific patient receiving a moderately emetogenic cancer chemotherapy regimen.
- Recommend antiemetic therapy for a specific patient receiving a highly emetogenic cancer chemotherapy regimen.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program provides 1 hour (0.1 CEU) of continuing education credit (program number 204-000-05-475-L01). Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official ASHP CE statements at the ASHP Advantage CE Processing Center at www.ashpadvantage.com.
Applying the Principles of Antiemetic Therapy to the Management of CINV: A Case-study Approach

Rowena N. Schwartz, Pharm.D., BCOP
Associate Professor, Pharmacy and Therapeutics
School of Pharmacy
University of Pittsburgh
Pittsburgh, Pennsylvania

Dr. Rowena Schwartz is Associate Professor and Vice Chair of Pharmacy and Therapeutics at the University of Pittsburgh School of Pharmacy and Coordinator, Pharmacy Programs at the University of Pittsburgh Cancer Institute (UPCI). In addition, Dr. Schwartz developed and currently directs the UPCI Cancer Pain Program and maintains an active clinical pharmacy practice at UPCI in the medical oncology, hematology, and bone marrow transplant adult inpatient care units.

Dr. Schwartz received a Bachelor of Science in Pharmacy degree from the College of Pharmacy, University of Illinois at the Medical Center in Chicago and her Doctor of Pharmacy at the University of Texas Health Science Center at San Antonio. She completed a two-year fellowship in oncology drug development at the University of Texas. Dr. Schwartz is a board-certified oncology pharmacist.

Dr. Schwartz’s research interest is in the use of novel drug therapy in the management of cancer and cancer-related complications with a focused interest in geriatric oncology. She is an active member of the American Society of Health-System Pharmacists, the Pennsylvania Society of Health-System Pharmacists, the American Association of Colleges of Pharmacy, the American College of Clinical Pharmacy, the Pennsylvania Cancer Pain Initiative, the Hematology and Oncology Pharmacy Association, the Geriatric Oncology Consortium, and the International Society of Oncology Pharmacy. In addition, Dr. Schwartz is a member of the Specialty Council on Oncology Pharmacy for the Board of Pharmaceutical Specialties. She has authored numerous book chapters, journal articles, and abstracts on various topics related to pharmacy practice in oncology.
Applying the Principles of Antiemetic Therapy to the Management of CINV: A Case-study Approach

Val R. Adams, Pharm.D., FCCP, BCOP
Associate Professor, Pharmacy Practice and Science
College of Pharmacy
University of Kentucky
Lucille P. Markey Cancer Center
Lexington, Kentucky

Dr. Val Adams is Associate Professor in the Division of Pharmacy Practice and Science in the College of Pharmacy at the University of Kentucky. He is part of the graduate faculty and staff member at the Markey Cancer Center, where he has a clinical practice site. As the director of the hematology/oncology residency program, Dr. Adams has trained twelve residents and maintains an active research lab. He received his B.S. degree in pharmacy from the University of Utah and received his Pharm.D. degree from the University of Texas at Austin jointly with the University of Texas Health Science Center at San Antonio. He completed a residency in hematology/oncology at the Audie L. Murphy Memorial V.A. Hospital in San Antonio, Texas and then completed a two-year fellowship in immunology and transplantation at the University of Florida. Following the completion of the fellowship, he joined the University of Kentucky faculty in 1996.
Applying the Principles of Antiemetic Therapy to the Management of CINV: A Case-study Approach

40th ASHP Midyear Clinical Meeting
Las Vegas, Nevada

Expensive New Antiemetics for Cancer Patients: Where Do They Belong in Therapy?

Val R. Adams, Pharm.D., FCCP, BCOP
Associate Professor, Pharmacy Practice and Science
University of Kentucky
Lucille P. Markey Cancer Center
Lexington, Kentucky

Objectives

At the conclusion of this program, participants should be able to:

◆ Define the current CINV problems.
◆ Describe the pathophysiology of CINV.
◆ Recommend CINV preventive treatment based on current guidelines.
CINV Rates


Palonosetron Trial HEC

Time to treatment failure = time to 1st emetic episode or use of rescue medication

PALO-99-05  HEC

Palonosetron Trial MEC

Time to treatment failure = time to 1st emetic episode or use of rescue medication

PALO-99-04 MEC
Is CINV Still A Problem?

**YES**

Types of Nausea and Vomiting

- **Anticipatory**
  - Pathophysiology
    - Learned response from prior therapy
  - Treatment
    - Best therapy is prevention of emesis during chemotherapy
    - Relaxation techniques shown to be effective
    - Benzodiazepines
      - Lorazepam usually beginning prior to chemotherapy or triggering event

- **Acute**
  - Chemo 24 hours

- **Delayed**
  - 24 hours

Time
**Acute GI Tract**

- CTZ = chemoreceptor trigger zone
- NTS = nucleus tractus solitarius
- D2, 5-HT3, NK1 = receptor abbrev.
- 5-HT3, NK1 = serotonin 3, neurokinin 1
- M = muscarinic
- H1 = histamine 1

**CTZ** = chemoreceptor trigger zone, **NTS** = nucleus tractus solitarius

**Receptor abbrev.**
- D2 = dopamine 2
- 5-HT3 = serotonin 3
- M = muscarinic
- H1 = histamine 1
- NK1 = neurokinin 1

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**Serotonin and Chemotherapy**

- **Cyclophosphamide**
- **Cisplatin**

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**Patterns of Acute Emesis**

- **Cisplatin**
- **Carboplatin**

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**Cubeddu LX. Oncology. 1996;53(suppl 1):18-25.**

**Martin M. Oncology. 1996;53(suppl 1):26-31.**
Delayed Nausea and Vomiting

- Pathophysiology unknown
- Pathologic findings
  - Altered GI motility
  - Normal levels of serotonin metabolites in the urine
  - Involves NK1 receptor stimulation in the CNS
  - Nausea and vomiting in acute phase increases risk
- Chemotherapy implicated: cisplatin, carboplatin, cyclophosphamide

Acute CINV Linked to Delayed CINV
Changing Beliefs

◆ CINV is still a problem, even with MEC
◆ Serotonin in the first 8 hours
◆ Substance P during 8–120 hours
◆ Traditional definition of acute and delayed does not match the physiology

MEC = moderately emetogenic chemotherapy

Prevention of CINV: Risk Factors

◆ Guideline considerations
  – Drug(s), dose(s), and rate of administration
  – Prior N/V with chemotherapy
◆ Other high-risk factors not incorporated in guidelines:
  – Young age, female, no alcohol history, concurrent radiation, history of N/V with pregnancy or motion sickness

Emetogenicity of Chemotherapy

◆ Based on percent of patients that will get sick if given no antiemetic
  
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<tr>
<td>5 (highly)</td>
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NCCN CINV Guideline

High (Level 5)
STARTING PRIOR TO CHEMOTHERAPY
1. Aprepitant 125 mg po d1, 80 mg po d2&3
2. Dex 12 mg po/iv d1, 8 mg po/iv d2-4
3. 5HT3 RA po/iv d1
 +/- Lorazepam 0.5 – 2 mg po/iv/subling q6h d1-4

NCCN CINV Guideline

Day 1
1. Dexamethasone
2. 5HT3 RA
 +/- Lorazepam
 +/- Aprepitant *

* carboplatin, cyclophosphamide, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate

Day 2-4
1a. Dexamethasone or
1b. 5HT3 RA or
1c. Metoclopramide or
1d. Aprepitant & dex **
 +/- Lorazepam

** Only if aprepitant used on d1

Moderate (Level 3–4)


NCCN CINV Guideline

Low (Level 2)  Minimal (Level 1)
1a. Dexamethasone or No Routine Prophylaxis
1b. Prochlorperazine or
1c. Metoclopramide*
 +/- Lorazepam

*Consider adding diphenhydramine

Assessing Response

◆ Primary Endpoint:
  – **Complete Response** = no emesis and no rescue medication
◆ Secondary Endpoints:
  – Frequency of vomiting episodes
  – Use of rescue therapy
  – Nausea
  – Quality of life (FLIE)

FLIE = functional living index emesis questionnaire

Case Studies:
Management of CINV in the Patient with Cancer

Rowena N. Schwartz, Pharm.D., BCOP
Associate Professor, Pharmacy and Therapeutics
School of Pharmacy
University of Pittsburgh
Pittsburgh, Pennsylvania

Val R. Adams, Pharm.D., FCCP, BCOP
Associate Professor, Pharmacy Practice and Science
University of Kentucky
Lucille P. Markey Cancer Center
Lexington, Kentucky

Case: Management of CINV in the Patient with Cancer

**JS is a 79-year-old male with NHL**

History of Present Illness:
• 2 months ago JS c/o SOB and cough
• s/p antibiotics without change in symptoms
• CXR: RUL mass ⇒ biopsy c/w NHL (DLBCL)
• s/p CHOP-R x 1
• Planned treatment: CHOP-R X 6 – 8

c/o = complaint of; SOB = shortness of breath; CXR = chest x-ray; RUL = right unilateral;
c/w = consistent with; NHL = non-Hodgkin's lymphoma; DLBCL = diffuse large B-cell lymphoma;
CHOP-R = cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone, plus rituximab
Case: Management of CINV in the Patient with Cancer

JS is a 79-year-old male with NHL (cont'd)

Past Medical History:
- Hypertension x 20 years (tx: benazepril 10 mg po QD)
- 25 pack-year smoking history
- Depression (tx: paroxetine 20 mg po QD)

Laboratory results:
- CBC WNL
- Electrolytes WNL
- Liver function test WNL
- Increased creatinine from baseline
  - SCr 2 weeks ago: 1.1 mg/dl
  - Current SCr: 1.8 mg/dl
- Glucose 190 mg/dl; HgA\textsubscript{C} pending

Presentation Today:
- s/p one course of chemotherapy
  - Pre-medication: dolasetron po
  - Discharge Rx for CINV: prochlorperazine prn
- Patient’s wife reports that JS experienced chronic nausea (˃4 days) that was not well managed with prochlorperazine
- Patient states he did not take prochlorperazine because of sedation
- Patient is concerned about ability to work during treatment

s/p = status post

Challenges of Antiemetic Therapy:
Maintaining the Individuals QOL
Case: Management of CINV in the Patient with Cancer

MP is a 42-year-old female with NHL

History of Present Illness:
- MS noted a swelling in her abdomen that progressively worsened ⇒ biopsy c/w NHL (DLBCL) about 16 months ago
- s/p CHOP-R x 6 with complete response
- Recently MP noted a new lymph node ⇒ evaluation demonstrated recurrent NHL
- Plan chemotherapy: ESHAP x 2 prior to auto HSCT transplantation

ESHAP = etoposide, methylprednisolone, high-dose ara-C, platinol; HSCT = hematopoietic stem cell transplant

Case: Management of CINV in the Patient with Cancer

MP is a 42-year-old female with NHL (cont’d)

Past Medical History:
- Insomnia (tx: trazadone 150 mg po q hs)
- Recent onset of hot flashes and irregular menses
- Anxiety (tx: pm lorazepam and behavioral therapy)
- Nausea history:
  - Significant nausea with last 2 cycles of CHOP
  - Nausea with pregnancy

Planned therapy:
- Etoposide 60 mg/m²/day IV daily x 4
- Methylprednisolone 500 mg IV daily x 5
- Cisplatin 25 mg/m²/day CI daily x 4
- Cytarabine 2 grams/m² IV x 1 on day 5

Case: Management of CINV in the Patient with Cancer

MP is a 42-year-old female with NHL (cont’d)

Social History:
- Recently divorced with 4 children (ages 10, 12, 14, 20)
- Occupation: investment banker
- Local support includes friends, a sister who lives locally, and ex husband
MK is a 27-year-old female s/p melanoma

History Present Illness:
- MK noted a mole on her shoulder about 6 months ago ⇒ when the mole bled she decided to get the mole removed; biopsy was consistent with cutaneous melanoma
- MK is currently participating in a trial that is evaluating the role of biochemotherapy as adjuvant therapy post resection

Past Medical History:
- Irritable bowel syndrome

Planned therapy:
- cisplatin 20 mg/m²/day IV daily x 4
- vinblastine 1.6 mg/m²/day IV daily x 4
- dacarbazine 800 mg/m² IV day 1
- aldesleukin 9 million international units / m² CI daily x 4
- interferon alfa 5 million units/m²/day subcutaneously days 1, 2, 3, 4, 5 and 7, 9, 11, 13

Social History:
- Married with one child (6 months)
- Occupation: works part time at office supply store and full-time college student
- Insurance coverage per husband (critical care nurse)
KZ is a 71-year-old female with multiple myeloma

History Present Illness:
- s/p femur fracture about 6 months ago ⇒ evaluation at that time suggestive of lytic lesions ⇒ evaluation consistent with MM (IgG)
- s/p thalidomide + dexamethasone ⇒ d/c neuropathy and constipation
- s/p DVD (doxil + vincristine + dex) x 4 cycles
- s/p mobilization with filgrastim
- s/p HSCT 8 days ago
  (preparative regimen: melphalan)

MM = metastatic melanoma

KZ is a 71-year-old female with multiple myeloma (cont’d)

Past Medical History:
- Diabetes x 40 years (tx: insulin)
- Anxiety x 30+ years (tx: prn lorazepam)
- Hypercholesterolemia (tx: statin therapy d/c at transplant)
- s/p DVT at time of orthopedic surgery (anticoagulation held at this time ⇒ low platelets)
- Depression (tx: paroxetine 20 mg po QD)

DVT = deep vein thrombosis

KZ is a 71-year-old female with multiple myeloma (cont’d)

Presentation Today:
- Nausea/vomiting x 2 weeks
  - ↑ nausea 2 days post transplantation
  - vomiting x 4 in last 24 hours
- Mucositis ⇒ currently on hydromorphone PCA
- Febrile within the last 24 hours ⇒ current antibiotics include cefepime + fluconazole
- Patient is sleepy but oriented when awake
**Case: Management of CINV in the Patient with Cancer**

**JM is a 45-year-old female with recurrent breast cancer**

**History Present Illness:**
- Diagnosed with early stage breast cancer 4 years ago
  - ER- PR –
  - HER2Neu + (FISH)
- s/p lumpectomy + radiation
- JM noted lump in her breast ⇒ biopsy consistent with breast cancer
- Planned treatment:
  - Lumpectomy ⇒ radiation ⇒ chemotherapy ⇒ trastuzumab

ER = estrogen receptor; PR = progesterone receptor; FISH = fluorescence in situ hybridization

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**Case: Management of CINV in the Patient with Cancer**

**JM is a 45-year-old female with recurrent breast cancer (cont’d)**

**Past Medical History:**
- Hypothyroidism (tx: Synthroid®)

**Planned therapy:**
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² day 1

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**Case: Management of CINV in the Patient with Cancer**

**JM is a 45-year-old female with recurrent breast cancer (cont’d)**

**Social History:**
- Single with two children (ages 10 and 14)
- Occupation: self-employed owner of a chain of small diners throughout the Midwest
- Support system:
  - significant other x 3 years
  - extended family (including parents, 6 brothers and 2 sisters)
Questions and Discussion

We welcome your questions.
Staff will collect all written question cards.
Please approach the standing microphones in the aisle.
Please complete the program evaluation and hand to staff as you exit.
Thank you for your attention.
Join us again for CE in the Mornings.
References


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**Rowena N. Schwartz, Pharm.D., BCOP**
Dr. Schwartz reports that she serves on a speakers’ bureau for Merck, MGI Pharma, and sanofi aventis and as a consultant for Merck and MGI Pharma.

**Val R. Adams, Pharm.D., FCCP, BCOP**
Dr. Adams reports that he serves on a speakers’ bureau for Merck and Roche.