Antiemesis: A Comparison of Treatment Approach between NCCN and ASCO Guidelines

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Objectives

1. Discuss the differences and similarities between antiemesis guidelines used for the prevention/treatment of chemotherapy induced nausea and vomiting (CINV)
2. Develop a prevention and management approach to optimally control CINV in patients being treated for cancer

Background

- **CINV has been consistently demonstrated to be among the most feared adverse effects of cancer treatment**
  - **Optimally preventing this side-effect is essential for decreasing need for dose-reductions, improving quality of life and ultimately improving outcomes**
- **Evidence Based Guidelines for Management of CINV:**
  - **American Society of Clinical Oncology (ASCO):** Last update July 13,2020
    - Antiemetics: ASCO Guideline Update | Journal of Clinical Oncology (ascopubs.org)
  - **National Comprehensive Cancer Network (NCCN):** Last update March 23,2022
    - Guidelines Detail (nccn.org)

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Principles of Emesis Control

- **Antiemetic regimens should be chosen based on:**
  - Drug with highest emetic risk in the chemotherapy regimen
  - Previous experience with antiemetics
  - Patient specific risk factors
- **Antiemetic prophylaxis should be given 30-60 minutes prior to chemotherapy and on a scheduled (not PRN) basis**
- **Patient needs to be protected throughout entire risk period**
  - Lasts at least 3 days for high emetic risk agents
  - Lasts 2 days for moderate emetic risk agents
- **Patient can adjust eating habits and adopt other lifestyle measures that may alleviate nausea and vomiting**

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Factors Affecting CINV

1. Specific therapeutic agents used
2. Dosage of the agents
3. Schedule and route of administration of the agents
4. Individual patient variability
   - Younger age
   - Female sex
   - Prior anticancer agents
   - History of little or no alcohol use
   - Morning sickness
   - Motion sickness
   - Anxiety

Although vomiting can often be prevented or decreased by using prophylactic antiemetic regimens, nausea is harder to control

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TYPES OF CINV

1. **Acute-onset**
   - Occurs within minutes to several hours after chemotherapy
2. **Delayed-onset**
   - Occurs in patients more than 24 hours after chemotherapy
   - Common with highly emetogenic chemotherapy (HEC)
3. **Anticipatory**
   - Occurs after a previous negative experience with chemotherapy
4. **Breakthrough**
   - Occurs despite prophylactic antiemesis treatment
   - Requires rescue antiemetics
5. **Refractory**
   - Resistant to optimization of antiemetics

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Delayed CINV

- **Delayed nausea/vomiting**: occurs from **24 hours to 5 days** after treatment
- **Chemotherapy Agents Associated:**
  - Cisplatin
  - Carboplatin
  - Cyclophosphamide
  - Doxorubicin

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Emetogenicity of Cancer Agents

- Frequency of anticancer agent-induced emesis depends on emetogenic potential of the chemotherapeutic agent used
- **Hesketh/Grunberg classification** divides chemotherapeutic agents into four levels according to the percentages of patients who experience acute emesis when they do NOT receive antiemetic prophylaxis
  - Updated each year by the NCCN panel with recently introduced drugs
  - ASCO uses same classification in their tables however not frequently updated

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Hesketh/Grunberg Classification

- **High emetic risk**: more than 90% of patients experience acute emesis
- **Moderate emetic risk**: more than 30-90% of patients experience acute emesis
- **Low emetic risk**: 10-30% of patients experience acute emesis
- **Minimal emetic risk**: fewer than 10% of patients experience acute emesis

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High Emetic Risk Agents: NCCN vs. ASCO

NCCN	ASCO
Anthracycline and Cyclophosphamide in combination	Anthracycline and Cyclophosphamide in combination
Carboplatin AUC ≥4, Cisplatin	Carmustine
Carmustine >250 mg/m2	Cisplatin
Sacituzumab govitecan-hziy	Cyclophosphamide >1500 mg/m2
Cyclophosphamide >1500 mg/m2	Dacarbazine
Dacarbazine	Mechlorethamine
Doxorubicin ≥ 60 mg/m2, Epirubicin >90 mg/m2	Streptozocin
Ifosfamide ≥2 g/m2 per dose	
Mechlorethamine, Melphalan ≥ 140 mg/m2	
Streptozocin	

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Take-Home Points: Classification of Cancer Agents

- Both guidelines classify by levels of emetogenicity however agents within those levels may differ depending on guideline used
- NCCN updated annually therefore better source for up-to-date classification of cancer agents emetogenic potential

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Classes of Anti-Emetics

1. **5-HT3 Antagonists (5-HT3 RA)**
   - ondansetron, granisetron, dolasetron
   - palonosetron
2. **NK1 Receptor Antagonists (NK1-RA)**
   - fosaprepitant
   - aprepitant
3. **Steroids**
   - dexamethasone
4. **Atypical antipsychotic**
   - olanzapine
5. **Benzodiazepines**
   - lorazepam
6. **Phenothiazines**
   - prochlorperazine
   - promethazine

High Emetic Risk: Anti-Emetic Agents Used

- **4-Drug Anti-Emetic Regimen recommended by both NCCN and ASCO Guidelines**
  - 5-HT3 RA, NK1-RA, Dexamethasone and Olanzapine
- **Both guidelines agree that when needed dexamethasone doses can be individualized**
  - Lower doses, frequency or even elimination of dexamethasone may be needed
- **NCCN guidelines recommend use of Dexamethasone 12 MG on Day 1 and 8 MG on Day 2-4 for high emetic risk however ASCO states the following:**
  - If patients do not receive an NK1-RA, the dexamethasone dose should be adjusted to 20 mg on Day 1 and 16 mg on days 2-4

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Olanzapine

- Atypical antipsychotic
- Antagonists of multiple receptors in CINV including: dopamine, seratonin, histamine, and acetylcholine-muscarine
- Effective in preventing acute and delayed emesis
- **NCCN update:** olanzapine can be substituted for dexamethasone if patient cannot tolerate dexamethasone
- **Common SE's**: fatigue, drowsiness, and sleep disturbances
- Increased risk for developing abnormal electrical activity (prolongation of QT interval)
- **Clinical Pearl:** Consider a dose of 5-mg if the previously given 10-mg dose caused excessive sedation
  - Sedation most common on Day 2
  - Improves over time

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Moderate: Anti-Emetic Agents Used

- **2-Drug Anti-Emetic Regimen recommended by ASCO Guidelines**
  - 5-HT3 RA and Dexamethasone
- **2-3 Drug Anti-Emetic Regimen recommended by NCCN Guidelines**
  - 5-HT3 RA and Dexamethasone (2 drug regimen)
  - 3-drug prophylactic regimen is recommended for select patients with additional risk factors or previous treatment failure to corticosteroid + 5-HT3 RA alone
- **Dosing of Dexamethasone on Day 1 differs between NCCN and ASCO Guidelines**
  - NCCN recommends Dexamethasone 12 MG on Day 1
  - ASCO recommends Dexamethasone 8 MG on Day 1
- **<u>Preferred</u> 5-HT3 RA in Moderate Emetic Risk Prevention**
  - NCCN states Palonosetron is the preferred 5-HT3 RA in this category
  - ASCO does NOT state a preferred 5-HT3 RA

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Carboplatin AUC ≥ 4

- NCCN lists this agent as high emetic risk therefore recommending a 4-Drug regimen for antiemesis prevention
- ASCO does NOT list it as high emetic risk rather moderate emetic risk however makes the following statement under moderate emetic risk category:
  - If the carboplatin AUC is ≥4, add an NK1-RA to the 5-HT3 RA and dexamethasone

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Dexamethasone Use with Checkpoint Inhibitors (CPIs)

- **CPIs include:**
  - Programmed death-1 (PD-1)
  - Programmed death 1-ligand (PD-L1)
  - Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4)
- CPIs are often used in combination with chemotherapy to treat many cancers
- Dilemma exists about using both concurrently due to potential of affecting the therapeutic efficacy of the CPIs via immunosuppressive effects
- **ASCO 2020 update provides guidance on this topic however NCCN does NOT**

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Dexamethasone

- Protection against CINV in both the acute and delayed setting
- Dexamethasone doses can be individualized; lower doses, change in frequency, or even elimination may be needed
  - Consider dexamethasone sparing strategies to limit side effects (such as insomnia and increase in glucose)
- **Clinical Pearl:** For patients suffering from extended delayed CINV, consider extending the course of dexamethasone. Also consider morning dosing to minimize insomnia

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Dexamethasone Use with Checkpoint Inhibitors (CPIs)

- **Guideline Question Asked:** Should current guideline-endorsed antiemetic regimens that include dexamethasone be modified when CPIs are incorporated in antineoplastic treatment regimens?
  - There is NO definitive data from clinical trials in adults to warrant omitting dexamethasone from prophylactic anti-emetic regimens when CPIs are administered in combination with chemotherapy
- **KEYNOTE 189 and KEYNOTE 407 Non-Small Cell Lung Cancer Trials**
  - Evaluated the role of chemotherapy in combination with pembrolizumab
  - Included dexamethasone as part of antiemetic regimen
  - Progression free survival and overall survival were significantly superior in the pembrolizumab arm

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Chimeric Antigen Receptor T Cell (CAR T-cell) Therapies

- ASCO guidelines does NOT address this topic
- **NCCN guidelines states the following:**
  - The NCCN Panel does **NOT** recommend the use of corticosteroids in antiemetic regimens for 3 to 5 days before and 90 days after CAR T-cell therapies, because corticosteroids **may decrease the persistence of the CAR T-cell population**

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Managing Multiday Emetogenic Chemotherapy Regimen

- **NCCN guidelines states the following:**
  - Acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy
  - Dexamethasone should be administered daily for both moderately and highly emetogenic chemotherapy then continued for 2-3 days after chemotherapy
  - Palonosetron 0.25 mg may be sufficient at the start of a 3-day chemotherapy regimen instead of given multiple doses of a short acting 5-HT3 RA

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Managing Multiday Emetogenic Chemotherapy Regimen

- **ASCO guidelines states the following:**
  - Adults treated with multiday antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agents given on each day and for 2 days after completion of the antineoplastic regimen
  - Adults treated with 4 or 5-day cisplatin regimens should be offered a 3-drug combination of an NK1-RA, a 5-HT3 RA, and dexamethasone

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Principles of Managing Breakthrough Emesis

- **NCCN guidelines state the following:**
  - It is much easier to prevent nausea/vomiting than it is to treat it
  - Approach to treating is to give an additional agent from a different drug class
  - Consider around the clock dosing rather than PRN
  - Pay special attention to anti-emetic regimen prior to next cycle with the goal of better preventing nausea and vomiting
    - NCCN gives multiple suggestions on this including use of olanzapine however does NOT have a preference on suggestions given
  - Consider antacid therapy if patient has dyspepsia (H2 blocker or proton pump inhibitor)

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Principles of Managing Breakthrough Emesis

- **ASCO guidelines state the following:**
  - If experiencing nausea and vomiting despite optimal prophylaxis, olanzapine can be added to their current anti-emetic regimen if not used in the past
  - If have already received olanzapine in the past and still experiencing nausea and vomiting then choose an agent from a different class

As opposed to NCCN guideline, ASCO guidelines give preference to addition of Olanzapine for breakthrough nausea and vomiting if unused in the past

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Cannabinoids

- **ASCO guideline state the following:**
  - There remains insufficient evidence for a recommendations regarding medical marijuana
  - Cannot recommend medical marijuana over the FDA approved cannabinoids dronabinol and nabilone
- **NCCN guideline states the following:**
  - Dronabinol and nabilone are cannabinoids that are approved by the FDA for refractory nausea and vomiting when patients have not responded to conventional antiemetics
    - **Clinical Pearl:** May stimulate appetite; to limit adverse effects, consider starting with lower doses and titrating to effect

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Clinical Pearls

- **NK1-RAs:**
  - Place in therapy is for prevention of CINV, NOT treatment of CINV and the most benefit seen is in the delayed CINV setting
- **5-HT3 RAs:**
  - After receiving any long acting 5-HT3 RAs (example: Palonosetron), short-acting agents such as ondansetron play a limited role for treating breakthrough nausea and vomiting; choose agent from a different class
- **Dexamethasone:**
  - For patients suffering from extended delayed CINV, consider extending the course of delayed dexamethasone as clinically appropriate
  - Consider morning dosing to minimize insomnia

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Clinical Pearls

- **Olanzapine:**
  - Consider a dose of 5 mg if the previously administered 10 mg dose caused excessive sedation
  - Consider 2.5 mg of olanzapine if patients report excessive sedation with 5 mg dose
  - Sedation is most prominent on Day 2 and improves over time (administer at bedtime when possible

Olanzapine CINV Prevention Dosing: 5 or 10 mg on day of chemotherapy followed by 5 or 10 mg once daily on days 2-4
Olanzapine CINV Treatment Dosing: 5 or 10 mg once daily for 3 days

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Summary

- **Experiencing CINV can not only affect a patient's quality of life but can also lead to:**
  - Dose reductions and/or unwillingness to continue treatment
  - Dehydration
  - Nutrient depletion
  - Decline of performance status
- **Ultimately, suboptimal control of CINV will lead to poor outcomes in our patients**
- Control of CINV in patients with cancer is critical and can effectively be done by referencing current guidelines and using clinical judgment as well as patient history to optimally prevent and/or treat this unfortunate side effect of chemotherapy

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Thank you!
Questions and/or Comments?

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