Antiemetics: ASCO Guideline Update

Hesketh & Kris et al.
Introduction


- The goals of this update are to provide oncologists, other healthcare practitioners, patients and caregivers with recommendations on:
  - The use of dexamethasone as a prophylactic antiemetic in patients receiving checkpoint inhibitors, and
  - Information on new antiemetics, antiemetic regimens and anticancer agent emetogenicity.
ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

• a systematic literature review by ASCO guidelines staff
• an expert panel provides critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by ASCO CPGC

The full ASCO Guideline methodology manual can be found at:

www.asco.org/guideline-methodology
Clinical Question

This guideline update addresses one clinical question:

1. Should current guideline-endorsed antiemetic regimens that include dexamethasone be modified when checkpoint inhibitors are incorporated in antineoplastic treatment regimens?
Target Population and Audience

Target Population
Adults and children who receive antineoplastic agents and adults who undergo radiation therapy for cancer.

Target Audience
Medical and radiation oncologists, oncology nurses, nurse practitioners, physician assistants, oncology pharmacists, and patients with cancer.
Summary of Recommendations

Adult Patients

*High-emetic-risk antineoplastic agents*

Adults treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of an NK₁ receptor antagonist, a serotonin (5-HT₃) receptor antagonist, dexamethasone, and olanzapine (day 1). Dexamethasone and olanzapine should be continued on days 2 to 4 (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Adults treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK₁ receptor antagonist, a 5-HT₃ receptor antagonist, dexamethasone, and olanzapine (day 1). Olanzapine should be continued on days 2 to 4 (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
Summary of Recommendations

**Moderate-emetic-risk antineoplastic agents**

Adults treated with carboplatin area under the curve (AUC) $\geq 4$ mg/mL/min should be offered a three-drug combination of an NK$_1$ receptor antagonist, a 5-HT$_3$ receptor antagonist, and dexamethasone (day 1) (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Adults treated with moderate-emetic-risk antineoplastic agents (excluding carboplatin AUC $\geq 4$ mg/mL/min) should be offered a two-drug combination of a 5-HT$_3$ receptor antagonist and dexamethasone (day 1) (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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Summary of Recommendations

**Moderate-emetic-risk antineoplastic agents (cont.)**
Adults treated with cyclophosphamide, doxorubicin, oxaliplatin and other moderate-emetic-risk antineoplastic agents known to cause delayed nausea and vomiting may be offered dexamethasone on days 2 to 3 (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

**Low-emetic-risk antineoplastic agents**
Adults treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT₃ receptor antagonist or a single 8-mg dose of dexamethasone before antineoplastic treatment (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).
Summary of Recommendations

**Minimal-emetic-risk antineoplastic agents**
Adults treated with minimal emetic risk antineoplastic agents should not be offered routine antiemetic prophylaxis (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

**Antineoplastic combinations**
Adults treated with antineoplastic combinations should be offered antiemetics appropriate for the component antineoplastic agent of greatest emetic risk (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
Summary of Recommendations

**Adjunctive drugs**
Lorazepam is a useful adjunct to antiemetic drugs, but is not recommended as a single-agent antiemetic (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

**Cannabinoids**
Evidence remains insufficient for a recommendation regarding medical marijuana for the prevention of nausea and vomiting in patients with cancer receiving chemotherapy or radiation therapy. Evidence is also insufficient for a recommendation regarding the use of medical marijuana in place of the tested and US Food and Drug Administration-approved cannabinoids dronabinol and nabilone for the treatment of nausea and vomiting caused by chemotherapy or radiation therapy.
Summary of Recommendations

**Complementary and alternative therapies**
Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure, and other complementary or alternative therapies for the *prevention* of nausea and vomiting in patients with cancer.

**High-dose chemotherapy with stem-cell or bone marrow transplantation**
Adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation should be offered a three-drug combination of an NK₁ receptor antagonist, a 5-HT₃ receptor antagonist, and dexamethasone (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
Summary of Recommendations

High-dose chemotherapy with stem-cell or bone marrow transplantation (cont.)

(New) A four-drug combination of an NK1 receptor antagonist, a 5-HT\textsubscript{3} receptor antagonist, dexamethasone, and olanzapine may be offered to adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation. (Type: evidence based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Multi-day antineoplastic therapy

Adults treated with multi-day antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agent given on each day of the antineoplastic treatment and for 2 days after completion of the antineoplastic regimen (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
Summary of Recommendations

Multi-day antineoplastic therapy (cont.)
Adults treated with 4- or 5-day cisplatin regimens should be offered a three-drug combination of an NK1 receptor antagonist, a 5-HT₃ receptor antagonist, and dexamethasone (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Breakthrough nausea and vomiting
For patients with breakthrough nausea or vomiting, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; and ascertain that the best regimen is being administered for the emetic risk (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).
Summary of Recommendations

**Breakthrough nausea and vomiting (cont.)**

Adults who experience nausea or vomiting despite optimal prophylaxis, and who did not receive olanzapine prophylactically, should be offered olanzapine in addition to continuing the standard antiemetic regimen (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Adults who experience nausea or vomiting despite optimal prophylaxis, and who have already received olanzapine, may be offered a drug of a different class (e.g. an NK₁ receptor antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol, or nabilone) in addition to continuing the standard antiemetic regimen (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate for dronabinol and nabilone, low otherwise; Strength of recommendation: moderate).
Summary of Recommendations

**Anticipatory nausea and vomiting**

All patients should receive the most active antiemetic regimen appropriate for the antineoplastic agents being administered. Clinicians should use such regimens with initial antineoplastic treatment, rather than assessing the patient’s emetic response with less effective antiemetic treatment. If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic desensitization (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

**High emetic risk radiation therapy**

Adults treated with high-emetic-risk radiation therapy should be offered a two-drug combination of a 5-HT₃ receptor antagonist and dexamethasone before each fraction and on the day after each fraction, if radiation therapy is not planned for that day (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
**Summary of Recommendations**

**Moderate emetic risk radiation therapy**

Adults treated with moderate-emetic-risk radiation therapy should be offered a 5-HT$_3$ receptor antagonist before each fraction, with or without dexamethasone before the first five fractions (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate).

**Low emetic risk radiation therapy**

Adults treated with radiation therapy to the brain should be offered breakthrough dexamethasone therapy. Patients who are treated with radiation therapy to the head and neck, thorax, or pelvis should be offered breakthrough therapy with a 5-HT$_3$ receptor antagonist, dexamethasone, or a dopamine receptor antagonist (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).
Summary of Recommendations

**Minimal emetic risk radiation therapy**

Adults treated with minimal emetic risk radiation therapy should be offered breakthrough therapy with a 5-HT₃ receptor antagonist, dexamethasone, or a dopamine receptor antagonist (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).
Summary of Recommendations

Concurrent radiation and antineoplastic agent therapy
Adults treated with concurrent radiation and antineoplastic agents should receive antiemetic therapy appropriate for the emetic risk level of the antineoplastic agents, unless the risk level of the radiation therapy is higher. During periods when prophylactic antiemetic therapy for the antineoplastic agents has ended, and ongoing radiation therapy would normally be managed with its own prophylactic therapy, patients should receive prophylactic therapy appropriate for the emetic risk of the radiation therapy until the next period of antineoplastic therapy, rather than receiving breakthrough therapy for the antineoplastic agents as needed (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
Summary of Recommendations

**Pediatric Patients**

*High-emetic-risk antineoplastic agents*

(Updated) Pediatric patients treated with high-emetic-risk antineoplastic agents should be offered a three-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant or fosaprepitant (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

(Updated) Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive aprepitant or fosaprepitant should be offered a two-drug combination of a 5-HT3 receptor antagonist and dexamethasone (Type evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
Summary of Recommendations

High-emetic-risk antineoplastic agents (cont.)
(Updated) Pediatric patients treated with high-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of palonosetron and aprepitant or fosaprepitant (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Moderate-emetic-risk antineoplastic agents
Pediatric patients treated with moderate-emetic-risk antineoplastic agents should be offered a two-drug combination of a 5-HT₃ receptor antagonist and dexamethasone (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
Summary of Recommendations

**Moderate-emetic-risk antineoplastic agents (cont.)**

(Updated) Pediatric patients treated with moderate-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of a 5-HT₃ receptor antagonist and aprepitant or fosaprepitant (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak).

**Low-emetic-risk antineoplastic agents**

Pediatric patients treated with low-emetic-risk antineoplastic agents should be offered ondansetron or granisetron (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).
Summary of Recommendations

*Minimal-emetic-risk antineoplastic agents*

Pediatric patients treated with minimal emetic risk antineoplastic agents should not be offered routine antiemetic prophylaxis (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).
Chemotherapy-induced nausea and vomiting (CINV) have been consistently demonstrated to be among the most feared adverse effects of cancer treatment.

Corticosteroids, almost exclusively dexamethasone, have been shown to be effective and safe agents for use either as single agents with low emetogenic chemotherapy or as essential components of multi-agent combination antiemetic regimens with moderate and highly emetogenic chemotherapy.

Checkpoint inhibitors have recently become an integral component of antineoplastic treatment in a variety of settings. Some theoretical concerns have been expressed that concurrent corticosteroid use might potentially compromise the antineoplastic efficacy of CPIs. No definitive data is currently available to prove or disprove this hypothesis.
Discussion

- The 2017 ASCO Antiemetic Guideline update listed both atezolizumab and ipilimumab in the low emetic risk category.

- Based on available updated data, it is recommended that these agents and all other approved anti PD-1, anti PD-L1 & the anti CTLA-4 agent ipilimumab now be listed as minimally emetogenic.

- No new antiemetic agents have been introduced since the 2017 antiemetic update.

- Intravenous formulations of aprepitant and netupitant-palonosetron were approved by the FDA for the treatment of chemotherapy induced emesis in 2018, and a 5 mg dose of olanzapine has been shown to be safe and effective when used in combination with a 5-HT₃ receptor antagonist, dexamethasone and an NK1 receptor antagonist with highly emetogenic chemotherapy.

- Olanzapine also showed promising efficacy in the setting of high-dose chemotherapy and stem cell transplantation and is an option to be added to the combination of a 5-HT₃ receptor antagonist, an NK1 receptor antagonist and dexamethasone.
Additional Resources

More information, including a Data Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/supportive-care-guidelines

Patient information is available at www.cancer.net
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