

Corticosteroids in the Treatment of Chemotherapy-Induced Nausea and Vomiting

Sally Yowell Barbour, PharmD, BCOP, CPP, *Durham, North Carolina*

Abstract

Chemotherapy-induced nausea and vomiting (CINV) is one of the most feared side effects of cancer treatment, despite the advances over the past decades. Corticosteroids have been shown to be effective in the management of CINV. These agents are usually used in combination with serotonin antagonists and neurokinin-1 antagonists for highly or moderately emetogenic chemotherapy or as monotherapy for low-emetogenic chemotherapy. Consensus guidelines provide guidance regarding the scenarios in which corticosteroids are recommended. This article reviews the mechanism of action, role, and safety of corticosteroids in the management of CINV. (*JNCCN* 2012;10:493–500)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Assess the classification of CINV
- Distinguish chemotherapy agents associated with high rates of CINV
- Analyze the use of corticosteroids in the treatment of acute CINV
- Analyze the use of corticosteroids in the treatment of delayed CINV

Chemotherapy-induced nausea and vomiting (CINV) is one of the most feared side effects of cancer treatment and is a cause of great distress for many patients.¹ In rankings of symptoms, vomiting and/or nausea has always been at the top (Table 1)^{1–5}; although with recent advances in treatment and control of vomiting, nausea continues to be the more problematic symptom. In fact, in a recent survey of women receiving cisplatin-based chemotherapy for gynecologic malignancies, the

From the Department of Pharmacy, Duke University Medical Center, Durham, North Carolina.

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Correspondence: Sally Yowell Barbour, PharmD, BCOP, CPP, Department of Pharmacy, Duke University Medical Center, DUMC 3089, Durham, NC 27710. E-mail: sally.yowell@duke.edu

EDITOR

Kerrin M. Green, MA, Assistant Managing Editor, *Journal of the National Comprehensive Cancer Network*

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AUTHORS AND CREDENTIALS

Sally Yowell Barbour, PharmD, BCOP, CPP, Department of Pharmacy, Duke University Medical Center, Durham, North Carolina

Disclosure: Sally Yowell Barbour, PharmD, BCOP, CPP, has disclosed no relevant financial relationships.

CME AUTHOR

Charles P. Vega, MD, Health Sciences Clinical Professor; Residency Director, Department of Family Medicine, University of California, Irvine

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Table 1 Patient Perceptions of the Most Severe Side Effects of Cancer Chemotherapy

Rank	1983 (Coates et al. ²)	1996 (Griffin et al. ³)	1997 (de Boer-Dennert et al. ¹)	1999 (Lindley et al. ⁴)	2004 (Hofman et al. ⁵)
1	Vomiting	Nausea	Nausea	Nausea	Fatigue
2	Nausea	Constantly tired	Hair loss	Hair loss	Nausea
3	Hair loss	Hair loss	Vomiting	Constantly tired	Sleep disturbances
4	Thought of treatment	Effect of family	Constantly tired	Vomiting	Weight loss
5	Length of treatment	Vomiting	Injections	Taste changes	Hair loss

potential for uncontrolled CINV ranked just above death as a cause of symptom distress.⁶ In addition to the distress and impairment of quality of life CINV causes patients, it can lead to serious complications, such as dehydration, electrolyte abnormalities, Mallory-Weiss tears, compromised ability to deliver chemotherapy, and increased hospital costs.⁷ Although many advances have been made in understanding the origin and pathophysiology of CINV and in the development of new agents, it is still an issue of concern for many patients and clinicians.

CINV Classification, Emetogenicity, and Risk Factors

Classification of CINV

In evaluating the use of antiemetics in the treatment of CINV, the classifications and origin of CINV are important to understand. CINV has 5 classifications, with acute and delayed the 2 major ones, in addition to anticipatory, breakthrough, and refractory. Acute CINV has been most commonly described as occurring within 24 hours of chemotherapy administration, with some agents causing emesis within a few hours. Delayed CINV occurs more than 24 hours after chemotherapy administration, although with some agents it can start as soon as 16 hours after administration. Delayed CINV most commonly lasts up to 3 days after treatment, but can sometimes last up to 7 days. Anticipatory CINV is a conditioned response and is most commonly associated with poor emetic control while on prior therapies, although it also can occur in patients before initial therapy. Sensory, olfactory, environmental, and gustatory factors are also associated with anticipatory CINV. Breakthrough and refractory CINV refer to situations in which patients continue to have CINV despite appropriate prophylactic mea-

asures or continue to have CINV that is not responsive despite appropriate interventions. One of the basic tenets of CINV management is to provide patients with appropriate antiemetic prophylaxis to cover the entire risk period, both acute and delayed. Failure to do so increases the likelihood of CINV in the first cycle, delayed emesis and anticipatory CINV, and poor control in subsequent cycles.⁷

Emetogenicity of Chemotherapy and Risk Factors

The emetogenicity of agents varies significantly and is the most significant factor in evaluating risk for CINV. In addition to the emetogenicity of the drug itself, other treatment-related factors, such as dose, route of administration, combination therapy, and schedule, contribute to the overall risk.⁸⁻¹¹ Patient risk factors must also be evaluated and include age, gender, alcohol consumption, prior CINV, and anxiety.^{8-10,12} Several methods have been used to categorize agents based on emetogenicity; however, most consensus and international guidelines use the following classification levels: high (> 90% chance of CINV without prophylaxis), moderate (30%–90% chance of CINV without prophylaxis), low (10%–30% chance of CINV without prophylaxis), and minimal (< 10% chance of CINV without prophylaxis). Commonly used highly emetogenic agents include cisplatin, perhaps the most well-known; the combination of an anthracycline and cyclophosphamide; and dacarbazine. Commonly used agents in the moderate category include carboplatin, irinotecan, oxaliplatin, cyclophosphamide, doxorubicin, and cytarabine (Table 2).

CINV Prophylaxis: Mechanism and Role of Corticosteroids

Serotonin receptor antagonists (5HT₃-RA), neurokinin-1 (NK1) receptor antagonists, and cor-

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Table 2 Emetogenicity of Intravenous Chemotherapeutic Agents

High (> 90% Chance of CINV Without Prophylaxis)			
AC combination (doxorubicin or epirubicin with cyclophosphamide)		Doxorubicin (> 60 mg/m ²)	
Carmustine (> 250 mg/m ²)		Epirubicin (> 90 mg/m ²)	
Cisplatin (≥ 50 mg/m ²)		Ifosfamide (≥ 10 g/m ²)	
Cyclophosphamide (> 1500 mg/m ²)		Mechlorethamine	
Dacarbazine		Streptozocin	
Moderate (30%–90% Chance of CINV Without Prophylaxis)			
Amifostine (> 300 mg/m ²)		Daunorubicin	
Arsenic trioxide		Doxorubicin (≤ 60 mg/m ²)	
Azacitidine		Epirubicin (≤ 90 mg/m ²)	
Bendamustine		Idarubicin	
Busulfan		Ifosfamide (< 10 g/m ²)	
Carboplatin		Interferon (≥ 10 million IU/m ²)	
Carmustine (≤ 250 mg/m ²)		Interleukin-2 (> 12–15 million IU/m ²)	
Cisplatin (< 50 mg/m ²)		Irinotecan	
Clofarabine		Melphalan	
Cyclophosphamide (≤ 1500 mg/m ²)		Methotrexate (250 to > 1000 mg/m ²)	
Cytarabine (> 200 mg/m ²)		Oxaliplatin	
Dactinomycin		Temozolomide	
Low (10%–30% Chance of CINV Without Prophylaxis)			
Amifostine (≤ 300 mg/m ²)		Liposomal doxorubicin	
Cabazitaxel		Methotrexate (> 50 to < 250 mg/m ²)	
Cytarabine (100–200 mg/m ²)		Mitomycin	
Docetaxel		Mitoxantrone	
Eribulin		Paclitaxel	
Etoposide		Paclitaxel-albumin	
5-Fluorouracil		Pemetrexed	
Floxuridine		Pralatrexate	
Gemcitabine		Pentostatin	
Interferon (> 5 to < 10 million IU/m ²)		Romidepsin	
Interleukin-2 (≤ 12 million IU/m ²)		Thiotepa	
Ixabepilone		Topotecan	
Minimal (< 10% Chance of CINV Without Prophylaxis)			
Alemtuzumab	Cytarabine (< 100 mg/m ²)	Methotrexate (≤ 50 mg/m ²)	Temsirolimus
Asparaginase	Decitabine	Nelarabine	Trastuzumab
Bevacizumab	Denileukin diftitox	Ofatumumab	Valrubicin
Bleomycin	Dexrazoxane	Panitumumab	Vinblastine
Bortezomib	Fludarabine	Pegaspargase	Vincristine
Cetuximab	Interferon (≤ 5 million/units/m ²)	Peginterferon	Vinorelbine
Cladribine	Ipilimumab	Rituximab	

Abbreviation: CINV, chemotherapy-induced nausea and vomiting.
Data from Refs.^{8–10}

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ticosteroids are the main agents used in the prevention and treatment of CINV. Additional agents available in the clinicians' armamentarium are dopamine antagonists, cannabinoids, benzodiazepines, and miscellaneous agents, such as olanzapine. Dexamethasone is the most widely used corticosteroid in the treatment of CINV, and methylprednisolone has also been studied and used. Both corticosteroids are effective as monotherapy and in combination with other agents, either with a serotonin antagonist alone or as part of a triple-drug regimen with an NK1 antagonist. They are recommended agents in both the acute and delayed settings.⁸⁻¹⁰

Mechanism of Action

The mechanism of action of corticosteroids in CINV remains relatively unknown. Studies in pigeons suggest that the antiemetic effect of steroids may be partially from their activity in the central nervous system.¹³ Evidence also suggests that the effect may be from activation of glucocorticoid receptors in the nucleus of the solitary tract in the medulla.¹⁴ Lastly, dexamethasone and methylprednisolone have also been shown to antagonize 5HT_{3A} receptors in *Xenopus* oocytes; this antagonism may also explain the beneficial effects of corticosteroids in CINV prophylaxis and treatment.¹⁵

Role in Management

Acute CINV: The role of corticosteroids in acute CINV management is largely in combination with either a 5HT₃ antagonist alone or as part of triple-drug therapy with an NK1 antagonist. In the moderately

emetogenic setting, when used in combination with a 5HT₃ antagonist, the optimal dexamethasone dose is 8 mg (Table 3). This dose was established by the Italian Group for Antiemetic Research in a study of 587 patients receiving carboplatin, cyclophosphamide, or anthracyclines. Patients were randomized to receive 1 of 3 dexamethasone treatments in combination with ondansetron, 8 mg intravenously: 8 mg intravenously before chemotherapy plus 4 mg orally every 6 hours for 4 doses, starting at the same time of the chemotherapy; 24 mg intravenously as a single dose before chemotherapy; or 8 mg intravenously as a single dose before chemotherapy. All patients received oral dexamethasone, 4 mg twice daily from days 2 to 5. The rates of complete protection against vomiting/nausea were not significantly different among the 3 dosing arms (84.6%/66.7%; 83.6%/56.9%; 89.2%/61.0%), nor was a significant difference seen in delayed control (81.0%/46.7%; 81.3%/45.1%; 79.8%/46.1%).¹⁶

In the highly emetogenic chemotherapy setting, before the introduction of routine combination with NK1 antagonists, when used in combination with a 5HT₃ alone, the recommended dose of dexamethasone was 20 mg. A study by the Italian Group for Antiemetic Research evaluated various single intravenous doses of dexamethasone (4, 8, 12, or 20 mg) in combination with ondansetron, 8 mg intravenously in patients receiving cisplatin. Complete protection from acute vomiting and nausea was significantly superior with the 20-mg dose compared with the 4- and 8-mg doses (83.2%/71% vs. 69.2%/60.9% and 69.1%/61%), and superior, but not significantly, to the

Table 3 Corticosteroid Dosing Recommendations

	NCCN	ASCO	MASCC
<i>High</i>			
• Acute	12 mg po or IV	12 mg po or IV	20 mg (12 mg if used with an NK1 antagonist)
• Delayed	8 mg po days 2-4 or 8mg po day 2, 8 mg twice daily days 3 and 4 ^a	8 mg po or IV; days 2-3 or days 2-4	8 mg bid for 3-4 d (qd with NK1 antagonist)
<i>Moderate</i>			
• Acute	12 mg po or IV	8 mg po or IV	8 mg
• Delayed	8 mg po or IV days 2 and 3	8 mg po or IV days 2 and 3	8 mg for 2-3 d
<i>Low</i>	12 mg po or IV	8 mg po or IV	4-8 mg

All corticosteroid doses for moderate and high regimens are in combination with a 5HT₃ antagonist +/- a neurokinin-1 antagonist.

Abbreviations: IV, intravenous; MASCC, Multinational Association of Supportive Care in Cancer; NK1, neurokinin-1.

^aWhen given with fosaprepitant, 150 mg IV.

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12-mg dose (78.5%/66.9%).¹⁷ With the introduction of the NK1 antagonists, the triple-drug combination has become the standard of care for highly emetogenic regimens. When this combination is used, the dose of the steroid is reduced to account for the interaction with CYP3A4, which increases the area under the curve of the corticosteroid by approximately 50%. The dose of dexamethasone in this triple-drug regimen is reduced to 12 mg for acute management of CINV. Corticosteroids are also an option for monotherapy in low emetogenic regimens, especially in patients who would be receiving it for hypersensitivity prophylaxis (e.g., paclitaxel; Table 3).

Delayed CINV: Dexamethasone is also recommended for the management of delayed CINV in both high and moderately emetogenic chemotherapy regimens. Doses are generally 8 mg once or twice daily in the delayed setting, depending on emetogenicity and concurrent antiemetics (Table 3). More recent data have suggested that corticosteroids could be eliminated from the delayed setting without decreased efficacy in CINV control in some settings. Aapro et al.¹⁸ evaluated 300 chemotherapy-naïve female patients receiving AC/EC (anthracycline and cyclophosphamide/epirubicin and cyclophosphamide)-based chemotherapy. All patients received a single injection of palonosetron, 0.25 mg intravenously in combination with dexamethasone, 8 mg intravenously on day 1 and were then randomized to either dexamethasone, 4 mg orally twice daily or placebo for days 2 and 3. The primary end point was complete response (no emesis and no rescue medication) in the overall (days 1–5) period. Overall complete response was achieved in 53.7% of the group receiving palonosetron plus dexamethasone days 1 through 3 and in 53.6% of the group receiving palonosetron plus dexamethasone on day 1. The authors concluded that a single injection of palonosetron and dexamethasone on day 1 might be a sufficient treatment option, and that reducing dexamethasone was not associated with significant reduction in antiemetic control during the 5-day period, or with an impact on patient functioning.

A similar study conducted by Celio et al.¹⁹ evaluated 332 chemotherapy-naïve patients receiving a variety of moderately emetogenic chemotherapy regimens, with oxaliplatin-based or anthracycline-containing regimens the most common. Patients received a single 0.25-mg injection of palonosetron in combination with dexamethasone, 8 mg intrave-

nously on day 1 and were then randomized to either 8 mg of oral dexamethasone daily or placebo for days 2 and 3. Noninferiority was shown, with overall complete response rates of 67.5% for those administered dexamethasone only on day 1, and 71.1% for those also administered dexamethasone on days 2 and 3. The authors concluded that palonosetron plus single-dose dexamethasone administered before common moderately emetogenic chemotherapy regimens protects against acute and delayed CINV, which is noninferior to that of palonosetron plus dexamethasone for 3 days, and that the major benefit of the single-day regimen occurred in patients receiving non-AC moderately emetogenic chemotherapy regimens.¹⁹ A single-day administration of triple-drug therapy (dexamethasone, fosaprepitant, and palonosetron) was also investigated in a small single-arm study,²⁰ which, if proven to be similar in efficacy in randomized trials, would provide a more convenient and perhaps safe option for patients undergoing emetogenic chemotherapy.

Safety of Corticosteroids in CINV

Corticosteroids used in CINV as either monotherapy or in combination with other agents are generally very well tolerated. The most common side effects are transient elevations in glucose, insomnia, anxiety, and gastric upset. However, in most settings the duration of therapy with a corticosteroid is short and side effects can be managed, and the benefits are thought to outweigh any adverse effects. They are not completely benign, however, and, although uncommon, can decompensate diabetes, cause psychosis, or reactivate an ulcer.²¹ In a survey of 60 patients receiving moderately emetogenic chemotherapy with dexamethasone for acute and delayed CINV prophylaxis, patients reported moderate to severe problems with insomnia (45%), indigestion/epigastric discomfort (27%), agitation (27%), increased appetite (19%), weight gain (16%), and acne (15%) the week after chemotherapy.²² A theoretical concern has also been expressed about their use in patients undergoing immunosuppressive chemotherapy because of a potential increased risk for infection and interference with the antitumor effects of chemotherapy.^{21,23} Their use in the bone marrow transplant setting and in some hematologic malignancies remains provider- and institution-specific.

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Consensus Guidelines

Numerous consensus guidelines are available to help guide clinicians in managing CINV and hopefully ensure that patients are being treated with the minimal accepted standard of antiemetic prophylaxis.⁸⁻¹⁰ The NCCN, ASCO, and Multinational Association of Supportive Care in Cancer (MASCC) all have comprehensive guidelines available. These guidelines are developed by multidisciplinary panels of nurses, pharmacists, and physicians, and are based on available data and clinical expertise. All of these guidelines have been updated within the past year and are similar in their overall recommendations for preventing CINV. For highly emetogenic chemotherapy regimens, a 3-drug regimen consisting of a 5HT₃-RA (palonosetron is the preferred agent in the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Antiemesis only), an NK1 receptor antagonist, and dexamethasone on day 1 followed by dexamethasone and an NK1 antagonist is recommended (available in this issue; to view the most recent version of these guidelines, visit www.NCCN.org). If the single dose of fosaprepitant, 150 mg, is used, then no additional NK1 receptor antagonist is recommended. For AC regimens, all guidelines recommend a 3-drug regimen as described for acute prophylaxis, but ASCO and MASCC recommend an NK1 antagonist only for delayed CINV control. If an NK1 antagonist is not available for patients receiving AC, then palonosetron is the preferred 5HT₃ antagonist in the MASCC recommendations.

For moderately emetogenic chemotherapy regimens, all guidelines recommend a combination of a 5HT₃-RA and dexamethasone on day 1. Either dexamethasone or a 5HT₃-RA is recommended for delayed coverage. Palonosetron is the preferred serotonin antagonist in all guidelines; however, if an NK1 receptor antagonist is used in a moderately emetogenic regimen, any serotonin antagonist is acceptable.⁸⁻¹⁰

Conclusions

CINV, and particularly nausea, remains a significant concern for patients receiving chemotherapy. Corticosteroids continue to play a key role in the management of CINV, even with the development of NK1 receptor antagonists and second-generation 5HT₃ antagonists. This class of drug has been shown to have a significant impact on the control of CINV

and remains the backbone of most CINV prophylactic regimens. Several consensus guidelines are available to help clinicians choose where to most appropriately use these agents to achieve optimal results in CINV control. New dosing strategies continue to be investigated that may better help practitioners use these effective agents to improve or maintain efficacy, decrease side effects, and provide more convenient dosing options for patients.

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- Your patient is a 48-year-old woman treated with cisplatin-based chemotherapy for metastatic cervical cancer. She has experienced significant CINV with her initial treatment. What should you consider regarding the classification of CINV as you treat this patient?
 - Acute CINV occurs during the first 48 hours after chemotherapy
 - Delayed CINV usually lasts up to 3 days after treatment
 - Environmental and sensory factors have been demonstrated to be unrelated to anticipatory CINV
 - Antiemetic treatment should cover either the acute or delayed phase, but not both, to avoid medication overdosage
- Which of the following chemotherapy agents is associated with the highest risk for CINV?
 - Doxorubicin at doses < 60 kg/m²
 - Streptozocin
 - Interferon at doses of > 10 million IU/m²
 - Gemcitabine
- Which of the following statements regarding the use of corticosteroids to help reduce this patient's acute nausea and vomiting is most accurate?
 - Corticosteroids generally should not be combined with serotonin antagonists
 - The optimal dose of dexamethasone is 24 mg when used in combination with NK1 antagonists
 - There is a positive dose-response relationship between higher doses of corticosteroids and better nausea control
 - The dose of dexamethasone may be decreased in triple drug therapy for highly emetogenic chemotherapy regimens
- What else should you consider regarding the use of corticosteroids for delayed CINV?
 - Regular treatment for 3–5 days with dexamethasone is superior to one-time treatment with dexamethasone plus palonosetron
 - The normal dose of dexamethasone to prevent delayed CINV is 8 mg once or twice daily
 - Elevations in glucose frequently preclude corticosteroid therapy for CINV
 - Fatigue is the most common side effect of corticosteroid therapy

Activity Evaluation

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