

Fosaprepitant dimeglumine for the management of chemotherapy-induced nausea and vomiting: patient selection and perspectives

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) is a debilitating side effect of antineoplastic agents. Several treatment regimens are used to address this problem. Fosaprepitant is a neurokinin-1 receptor blocker used in the prevention and treatment of CINV, especially for moderately and severely emetogenic chemotherapy. It is highly effective in the treatment of delayed CINV. Data from previous studies show that fosaprepitant is noninferior to aprepitant in the management of CINV. Fosaprepitant is given as a single-dose intravenous infusion, thus offering better patient compliance. The dose-limiting side effect of fosaprepitant is an infusion-related reaction, ranging from pain at the infusion site to thrombophlebitis. This side effect has been reported with coadministration of anthracycline agents.

Keywords: chemotherapy nausea and vomiting, fosaprepitant, neurokinin inhibitor

Introduction

Cancer is the second leading cause of mortality in the United States after heart disease.¹ Over the years, cancer survival has significantly improved due to a better understanding of cancer biology and the availability of various forms of treatment. One of the core modalities in cancer treatment is chemotherapy. A dreaded side effect, however, is chemotherapy-induced nausea and vomiting (CINV). Treatment for CINV has evolved over the past 2 decades and includes supportive and pharmacologic treatment. Controlling CINV improves the patient's functional status, quality of life, and capacity to perform activities of daily living.^{2,3} Nonpharmacologic management of CINV that has been described includes yoga, music therapy, acupuncture, Concord grape, and ginger. A systematic review of these interventions has been done and showed insufficient evidence that the said interventions benefit patients with CINV. Non-pharmacologic interventions could be an adjunct given the low risk for toxicities.⁴ An important aspect in the management of CINV is patient education regarding the timing, prevention, and treatment of CINV.⁵ Several medications address the problem of acute and delayed CINV. The medications that are recommended vary with the emetogenic risk of a chemotherapeutic regimen. For highly emetogenic chemotherapy, a combination of a serotonin antagonist 5-hydroxytryptamine 3 (5-HT₃), dexamethasone, and neurokinin inhibitor has been recommended. Palonosetron combined with dexamethasone is preferentially used for moderately emetogenic regimens. For low-risk patients, prechemotherapy dexamethasone is offered.^{3,6} The introduction of neurokinin inhibitors has greatly improved the ability to prevent and treat persistent CINV in patients

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receiving moderate to highly emetogenic chemotherapy. This review will focus on the use of the neurokinin inhibitor, fosaprepitant, in the management of CINV.

Pathophysiology of CINV

CINV is brought about by a complex process involving interconnected neurological pathways, neurotransmitters, and receptors.⁷ Emetogenic receptors are concentrated in three locations in the brainstem: the vomiting center in the medulla oblongata, the chemoreceptor trigger zone in the area postrema in the floor of the fourth ventricle, and the nucleus of the solitary tract. These areas are rich in 5-HT₃, neurokinin-1 (NK-1), and dopamine (D) receptors. Serotonin, substance P, and dopamine bind to these receptors, respectively, to initiate the sensation of nausea and the vomiting reflex.⁸

The gastrointestinal tract is composed of mechanical and chemical receptors. Alterations in the chemical balance of different substances detected by chemoreceptors lead to the activation of vagal afferents, which leads to a cascade of events that then lead to nausea and vomiting.^{9,10} Most emetogenic antineoplastic drugs are toxic to the enterochromaffin cells lining the gastrointestinal tract that store and release serotonin. Exposure to these agents leads to the release of serotonin that binds to 5-HT₃ receptors in the gut, thereby activating the vagal afferents in the gut and brainstem.^{11,12}

The NK-1 receptor is the main receptor for the tachykinin family of peptides that includes substance P. Substance P has also been implicated in the pathogenesis of CINV.¹³ Substance P and NK-1 receptor are found in relevant sites (vagal afferent, nucleus tractus solitarius, and gastrointestinal mucosa) that are essential in the process of emesis. Binding of substance P to NK-1 receptors initiates a cascade of events causing nausea and vomiting. Various stimuli that activate this pathway include chemotherapeutic agents such as cisplatin, radiation, opioids, apomorphine, and electrical stimulation of abdominal vagal afferents. The anatomical localization of these sites has led to the development of antagonists against NK-1 receptor in the treatment of CINV.^{14,9}

CINV

CINV is a very common side effect of various antineoplastic agents. This greatly affects the quality of life of cancer patients.¹⁵ Risk factors identified for the development of CINV include female sex, alcohol use, and younger age.^{16–18} These risk factors also predict the failure of antiemetics for both prophylaxis and treatment of CINV (Table 1).

The risk of CINV also depends on the type of chemotherapy. The emetogenic potential is defined depending on

Table 1 Risk factors for CINV

Risk factors	Change in risk
Sex	Greater risk in females
Age	Lower incidence at <6 or >50 years
Alcohol consumption	Lower incidence in individuals consuming >10 alcohol units/week
Motion sickness	Prior history leads to greater risk
Pregnancy-induced emesis	Prior history leads to greater risk
Anxiety	High anxiety levels correlated with greater risk
Previous cycles of chemotherapy	Poorly controlled nausea and vomiting in previous cycles increases the likelihood of CINV and anticipatory nausea and vomiting

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Abbreviations: CINV, chemotherapy-induced nausea and vomiting.

Table 2 Emetogenic levels of antineoplastic drugs

Minimal risk	Low risk	Moderate risk	High risk
Bevacizumab	Bortezomib	Carboplatin	Carmustine
Bleomycin	Cetuximab	Cyclophosphamide (≤1.5 g/m ²)	Cisplatin
Busulfan	Cytarabine (≤100 mg/m ²)	Cytarabine (>1 g/m ²)	Cyclophosphamide (>1.5 g/m ²)
Cladribine	Docetaxel	Daunorubicin	Dacarbazine
Fludarabine	Etoposide	Epirubicin	Mechlorethamine
Vinblastine	Fluorouracil	Idarubicin	Streptozocin
Vincristine	Gemcitabine	Ifosfamide	
Vinorelbine	Ixabepilone	Irinotecan	
	Lapatinib	Oxaliplatin	
	Methotrexate		
	Mitomycin		
	Mitoxantrone		
	Paclitaxel		
	Pemetrexed		
	Temsirolimus		
	Topotecan		
	Trastuzumab		

Notes: From N Engl J Med; Hesketh PJ; Chemotherapy-induced nausea and vomiting; 358(23):2482–2494; Copyright © 2008 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.¹⁸

the level of risk: minimal risk (<10%), low risk (10%–30%), moderate risk (30%–90%), and high risk (>90%) (Table 2). CINV is classified based on the timing of occurrence: it may be acute if it occurs within initiation of chemotherapy (lasts <24 hours), delayed if it occurs after 24 hours (persisting for 6–7 days), or anticipatory (prior to chemotherapy administration).¹⁹

Fosaprepitant

Fosaprepitant (Emend for injection – Merck & Co., Inc., Kenilworth, NJ, USA; Ivemend – Merck Sharp & Dohme Ltd, Hertfordshire, Europe) is an NK-1 receptor antagonist that is approved for the treatment of CINV. It is an *N*-phosphoryl

Table 3 Drug interactions of (Fos)aprepitant: review of literature and implications for clinical practice

Drug class	Major CYP450 pathway	Comments
Antineoplastics	Alkylating agents (CYP3A4 inhibition) Cyclophosphamide Ifosphamide	Slight increase in blood levels but no clinically significant impact (cyclophosphamide); increases neurotoxicity with ifosphamide
	Topoisomerase inhibitor (CYP3A4 inhibition) Etoposide	Theoretical increase in blood levels that requires close clinical monitoring
	Microtubule inhibitor (CYP3A4 inhibition) Docetaxel/paclitaxel	Theoretical increase in blood levels that requires close clinical monitoring
	Tyrosine kinase inhibitor (CYP3A4 inhibition) Crizotinib Erlotinib	Theoretical increase in blood levels; increased levels noted with Erlotinib that can potentiate antitumor response
	Opioids	Opioids (CYP3A4 inhibition) Oxycodone Fentanyl Hydrocodone Methadone
Anticoagulants	Warfarin (CYP2C9 induction)	Decreases INR that requires close monitoring and increased dosing
	Apixiban/rivaroxaban (CYP3A4 inhibition)	Potential to increase bleeding that requires close monitoring

Notes: Adapted from Dushenkoy A, Kalabalik J, Carbone A, Jungsuwadee P. *J Oncol Pharm Pract*. Drug interactions with aprepitant or fosaprepitant: review of literature and implications for clinical practice. Epub February 25, 2016. Copyright © 2016 by SAGE Publications. Reprinted by permission of SAGE Publications, Ltd.²²

Abbreviation: INR, international normalized ratio.

derivative of aprepitant. The prodrug, fosaprepitant, is converted into the active aprepitant to exert its antiemetic properties.²⁰

It is converted into the active drug, aprepitant, in hepatic and extrahepatic tissues (kidney, lungs, and ileum). Aprepitant is able to cross the blood–brain barrier and block the NK-1 receptor that is widely distributed in the central nervous system. Fosaprepitant has a half-life of approximately 2.3 minutes, with plasma levels below the level of detection in 30 minutes. In the plasma, more than 95% of the drug is protein bound. The volume of distribution of both aprepitant and fosaprepitant is 70 L. Given the high volume of distribution, the drug stays in the body for a longer period of time, hence its efficacy for delayed CINV.²¹

Aprepitant is metabolized mainly by the CYP3A4, with minor metabolism via the CYP1A2 and CYP2C19. It is a moderate inhibitor of CYP3A4 and inducer of CYP2C9. In contrast, fosaprepitant is a weak inhibitor when administered as a single 150 mg intravenous infusion. This becomes important for patients who take drugs that are likewise metabolized through this process because coadministration will need dose adjustments (Table 3).^{21,22}

Fosaprepitant – the missing link in antiemesis for cancer patients

Aprepitant is one of the first NK-1 receptor antagonists approved for the prevention and management of nausea and vomiting brought about by moderately and highly emetogenic chemotherapy. It is conventionally administered orally for 3 days (125 mg on Day 1 and 80 mg for Days 2 and 3).

It is generally combined with a serotonin antagonist (5-HT₃) and dexamethasone. To improve compliance, the prodrug, fosaprepitant, was formulated. This is given as a single dose on Day 1 of chemotherapy as a 150 mg intravenous infusion. That single dose is able to block 90% of NK-1 receptors.^{21,23}

A study by Celio et al²¹ compared fosaprepitant and aprepitant in the management of acute and delayed CINV among patients treated with high-dose cisplatin. The results showed that fosaprepitant was noninferior to aprepitant. Both agents are highly efficacious for delayed CINV (nausea and vomiting after 24 hours of chemotherapy).²¹ A randomized, double-blind trial involving 2,322 patients receiving a cisplatin dose of >70 mg/m² compared aprepitant (with ondansetron and dexamethasone) and fosaprepitant (with ondansetron and dexamethasone). The majority of these patients had lung and gastrointestinal malignancy. The results showed that a single dose of fosaprepitant was noninferior to a 3-day course of aprepitant.²³

A 5-day course of aprepitant was compared with a single dose of fosaprepitant in patients receiving highly emetogenic chemotherapy (cisplatin dose >60 mg/m²). There was no significant difference in the efficacy of the incidence of nausea and vomiting 7 days after chemotherapy between the two groups.²⁴

Fosaprepitant has been compared to serotonin antagonist (5-HT₃) – dexamethasone combination, the most common regimen used to treat CINV. A Phase III randomized double-blind study compared a fosaprepitant regimen in combination with granisetron and dexamethasone vs granisetron and dexamethasone only. The end point of the study was a complete response defined as total absence of nausea and vomiting

Table 4 Summary of clinical trials on fosaprepitant

Study, location	Design	Study patients	Type of malignancy	Sample size	Intervention		Study period	Outcome	Fosaprepitant regimen	Conclusion
					Fosaprepitant regimen	Comparison				
Grunberg et al. ²³ Canada	Randomized double-blind noninferiority	Cisplatin based (≥ 70 mg/m ²) – HEC	Lung, GI, GU, breast	2,322	F + O + D	A + O + D	I–5 days post-chemo	CR*	71.9% vs 72.3%; (95% CI –4.1 to 3.3)	Noninferior
Saito et al. ²⁵ Japan	Randomized double-blind placebo-controlled superiority	Cisplatin based (≥ 70 mg/m ²) – HEC	Lung, GI, GU, head and neck	347	F + G + D	Pl + G + D	I–5 days post-chemo	CR*	64% vs 47%; P=0.001	Superior
Ando et al. ²⁴ Japan	Randomized open-label controlled noninferiority	Patients on cisplatin containing (≥ 60 mg/m ²) – HEC	Lung, GI, head and neck	93	F + P/G/Az + D	A + P/G/Az + D	I–7 days post-chemo	CR*	82.2% vs 85.4%; P=0.90	Noninferior
Weinstein et al. ²⁶ International	Randomized double-blind Phase III superiority	Non-AC chemotherapy regimen – MEC	Lung, GI, gynecologic, breast, head and neck	1,015	F + O + D	Pl + O + D	0–120 hours post-chemo	CR*	77.1% vs 66.9%; P<0.001	Superior
Nishimura et al. ²⁷ Japan	Randomized open-label controlled Phase III	Patients on oxaliplatin based – MEC	Colorectal	413	F/A + O + D	O + D	I–7 days post-chemo	No emesis	95.7% vs 83.6%; P<0.0001	Superior
Kitayama et al. ²⁸ Japan	Prospective randomized crossover	Patients on (oxaliplatin/irinotecan based) – MEC	Colorectal, breast	35	F + G + D	P + D	I–5 days post-chemo	CR*	69% vs 74%; P=0.56	Noninferior

Note: *No vomiting or use of rescue anti-emetics. **Abbreviations:** A, aprepitant; AC, adriamycin + cyclophosphamide; Az, azasetron; CI, confidence interval; CR, complete response; D, dexamethasone; F, fosaprepitant; G, granisetron; GI, gastrointestinal; GU, genitourinary; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; O, ondansetron; P, palonosetron; Pl, placebo; chemo, chemotherapy.

after a high dose of cisplatin. Overall, the fosaprepitant group had better complete response results (64% vs 47%). Fosaprepitant is effective in preventing both acute and delayed CINV, with a complete response of 94% and 65%, respectively.²⁵

Weinstein et al²⁶ studied the use of a single-dose fosaprepitant vs ondansetron with dexamethasone for the prevention of CINV. There was no significant difference in the complete response in the acute phase (93.2% vs 91%). However, in the delayed phase, fosaprepitant achieved higher complete response rates (78.9% vs 68.5%; P<0.001).²⁶

A study involving the use of aprepitant or fosaprepitant combined with a 5-HT3 antagonist and dexamethasone in colorectal cancer patients receiving oxaliplatin-based chemotherapy showed that the aprepitant/fosaprepitant group achieved better antiemetic outcomes in the overall response rate and prevention of delayed CINV.²⁷

Kitayama et al²⁸ did a prospective randomized crossover study to evaluate the efficacy of palonosetron with dexamethasone vs fosaprepitant with granisetron and dexamethasone in the prevention of CINV among patients receiving moderately emetogenic chemotherapy and found no significant difference between the two groups.

Taking into account all these data, fosaprepitant is effective in the management of CINV, particularly for patients receiving moderately and highly emetogenic chemotherapy. An important benefit is the ability of this medication to control delayed CINV that can develop in the days after chemotherapy administration (Table 4).⁵

Venous toxicity

Fosaprepitant, like its oral counterpart aprepitant, is associated with side effects. These usually include anorexia, constipation, nausea, vomiting, diarrhea, hiccups, and asthenia.^{23,25} In a study evaluating a single dose of fosaprepitant for the prevention of CINV that included 1,143 patients receiving the drug, the most commonly noted side effects included constipation (10.6%), asthenia (8.6%), diarrhea (7.8%), and vomiting (6.6%).²³ These adverse events were not significantly different from that of aprepitant. The study of Saito et al²⁵ that compared a fosaprepitant regimen to that of granisetron revealed that the most common adverse event of fosaprepitant was leukopenia, which accounted for 59.2% (103 out of 174) followed by anorexia (51.7%) and nausea (43.7%). Infusion site reaction is the major limiting adverse reaction during fosaprepitant administration. One study showed that 23.6% of patients receiving fosaprepitant developed an infusion site reaction.²⁵ These reactions include pain, erythema, swelling, extravasation, and phlebitis.²⁹

Table 5 Clinical practice guidelines in the management of chemotherapy-induced nausea and vomiting

	High emetic risk	Moderate emetic risk	Low emetic risk
ASCO ^a	NK-1 antagonist (aprepitant/fosaprepitant) + 5-HT3 antagonist (granisetron/ondansetron/palonosetron/dolasetron/tropisetron/ramosetron) + dexamethasone	Palonosetron + dexamethasone	Dexamethasone
NCCN ^b	NK-1 antagonist (aprepitant/fosaprepitant/rolapitant) + 5-HT3 antagonist (dolasetron/ondansetron/granisetron/palonosetron) + dexamethasone or Netupitant + palonosetron + dexamethasone or Olanzapine + palonosetron + dexamethasone	5-HT3 antagonist (dolasetron/ondansetron/granisetron/palonosetron) + dexamethasone with or without NK-1 antagonist (aprepitant/fosaprepitant/rolapitant) or netupitant + palonosetron + dexamethasone or olanzapine + palonosetron + dexamethasone	Dexamethasone or prochlorperazine or 5-HT3 antagonist (dolasetron/granisetron/ondansetron)
ESMO/ MASCC ^c	NK-1 antagonist (aprepitant/fosaprepitant) + 5-HT3 antagonist + dexamethasone	AC regimen NK-1 antagonist (aprepitant/ fosaprepitant) + 5-HT3 antagonist + dexamethasone Non-AC regimen palonosetron + dexamethasone	Dexamethasone or 5-HT3 antagonist or Dopamine antagonist

Notes: ^aData from Basch et al.⁶ ^bReferenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for NCCN Guidelines for Antiemesis V.2.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed March 31, 2016. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK[®], NCCN[®], NCCN GUIDELINES[®], and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.³⁵ ^cAdapted from Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Annals of Oncology*. 2010;21(Suppl 5):v232–v243. By permission of Oxford University Press on behalf of the European Society for Medical Oncology. This image/content is not covered by the terms of the Creative Commons license of this publication. For permission to reuse, please contact the rights holder. Copyright © 2010, Oxford University Press.³⁶

Abbreviations: ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network[®]; ESMO, European Society of Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; NK-1, neurokinin-1; 5-HT3, 5-hydroxytryptamine/serotonin; AC, anthracycline/cyclophosphamide.

In several studies, infusion site reactions have been associated with infusion of anthracycline-based chemotherapy. In a study by Sato et al,³⁰ fosaprepitant coadministered with an anthracycline-based regimen was associated with a higher incidence (67%) of infusion site reaction compared to regimens without anthracycline (16%). A comparison of fosaprepitant infusion with anthracycline vs a cisplatin-based regimen showed that the former resulted in significantly higher infusion site reaction with an odds ratio of 12.95.³¹ In a study comparing fosaprepitant versus aprepitant when administered with the combined doxorubicin and cyclophosphamide, fosaprepitant resulted in higher infusion site reaction, 34.7% vs 2.3%.³² The mechanism of fosaprepitant-induced venous toxicity with an anthracycline-based regimen is poorly understood. A possible hypothesis is that both anthracycline chemotherapy and fosaprepitant cause impaired endothelial function, thus leading to venous toxicity.³³ Thus, fosaprepitant should be avoided in patients receiving anthracycline, if possible. Otherwise, it should be administered with intravenous fluids in a proximal peripheral venous site as it has been associated with decreased chances of infusion site reaction.³⁴ There have been no studies looking into fosaprepitant administration through a central venous access.

Management of CINV

There is variation among the different clinical practice guidelines in the management of CINV. Different medical

oncology societies have published their own approach in treating CINV. These guidelines are summarized in Table 5.

Conclusion

CINV is a major dose-limiting side effect of cancer treatment. Fosaprepitant has been approved for the prevention and treatment of CINV caused by moderately and highly emetogenic chemotherapy. It was found to be more efficacious compared to serotonin antagonist – dexamethasone drug combination and is noninferior to aprepitant in the management of CINV. With single dosing, it offers better compliance. Infusion site reaction is a major side effect, especially when administered with an anthracycline-based regimen. Infusing in a more proximal peripheral site and with intravenous fluids appears to decrease the chances of venous toxicity.

Disclosure

The authors report no conflicts of interest in this work.

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