

Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain the optimal antiemetic prophylaxis for patients receiving chemotherapy in regard to the emetogenic potential of the therapy.
2. Describe the difference between acute and delayed emesis.
3. Discuss the properties and optimal use of the different antiemetic drugs.

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ABSTRACT

Clinicians should be aware that chemotherapy-induced nausea and vomiting (CINV) is still one of the most feared side effects of chemotherapy. With the correct use of antiemetics, CINV can be prevented in almost 70% to up to 80% of patients. Treatment guidelines are useful tools that enable physicians to integrate the latest clinical research into their practices. The large volume of rapidly evolving clinical data has been summarized and incorporated into treatment recommendations by well-known and reliable institutions, including the Mul-

tinational Association of Supportive Care in Cancer, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network. Despite the availability of such guidelines, however, there is evidence that adherence to and implementation of treatment recommendations are less than optimal. This review focuses, in particular, on the conformity and differences of these three guidelines. Furthermore, open questions and trends in the field of antiemesis are discussed as well. *The Oncologist* 2007;12:1143–1150

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INTRODUCTION

The goal of each antiemetic therapy is to abolish nausea and vomiting. Twenty years ago, nausea and vomiting were common adverse events of certain types of chemotherapy and forced up to 20% of patients to postpone or refuse potentially curative treatment [1]. Clinical and basic research over the past 25 years has led to steady improvements in the control of chemotherapy-induced nausea and vomiting (CINV). The development of the 5-HT₃-receptor antagonists (5-HT₃RAs) in the early 1990s was one of the most significant advances in the chemotherapy of cancer patients. Another group of antiemetics, the neurokinin₁-receptor antagonists (NK₁RA), has recently been developed, and the first drug in this class, aprepitant, was incorporated into the updated antiemetic guidelines.

In 1998, the first Multinational Association of Supportive Care in Cancer (MASCC) antiemetic guidelines based on the results of the Perugia consensus conference were published, followed by the American Society of Clinical Oncology (ASCO) guidelines in 1999 [2, 3]. Last year, these two guidelines, as well as the National Comprehensive Cancer Network (NCCN) guidelines, were updated [4–6]. This review compares these three guidelines with respect to the use of antiemetics.

CLASSIFICATION OF CINV

Agreement exists on how to classify CINV. CINV is differentiated into three categories: acute onset (mostly serotonin related), occurring within 24 hours of initial administration of chemotherapy; delayed onset (in part substance P related), occurring 24 hours to several days after initial treatment; and anticipatory, observed in patients whose emetic episodes are triggered by taste, odor sight, thoughts, or anxiety secondary to a history of poor response to antiemetic agents or inadequate antiemetic prophylaxis in the previous cycle of chemotherapy [7, 8].

EMETOGENICITY OF CHEMOTHERAPEUTIC AGENTS

The emetogenic potential of the chemotherapeutic agents used is the main risk factor for the degree of CINV. In regard to their emetogenic potential, the chemotherapeutic agents are classified into four emetic risk groups: high (90%), moderate (30%–90%), low (10%–30%), and minimal (<10%), as suggested by all three guidelines (the figures in parentheses represent the percentage of patients having emetic episode(s) when no prophylactic antiemetic protection provided) [4–6]. Hence, antiemetic prophylaxis is directed toward the emetogenic potential of the chemotherapy (Table 1 and Table 2). In the MASCC guidelines, in

Table 1. Emetogenic risk of i.v. chemotherapeutic agents [4–6]

High (emesis risk, >90% without antiemetics)	
Carmustine, BCNU	Lomustine
Cisplatin	Mechlorethamine
Cyclophosphamide (>1,500 mg/m ²)	Pentostatin
Dacarbazine, DTIC	Streptozotocin
Dactinomycin, actinomycin D	
Moderate (emesis risk, 30%–90% without antiemetics)	
Altretamine	Ifosfamide
Carboplatin	Irinotecan
Cyclophosphamide (<1,500 mg/m ²)	Melphalan
Cytarabine (>1 g/m ²)	Mitoxantrone (>12 mg/m ²)
Daunorubicin	Oxaliplatin
Doxorubicin	Temozolomide
Epirubicin	Trabectedin
Idarubicin	Treosulfan
Low (emesis risk, 10%–30% without antiemetics)	
Asparaginase	Mitoxantrone (<12 mg/m ²)
Bortezomib	Paclitaxel
Cetuximab	Pegasparginase
Cytarabine (<1g/m ²)	Pemetrexed
Docetaxel	Teniposide
Etoposide	Thiopeta
5-Fluorouracil	Topotecan
Gemcitabine	Trastuzumab
Methotrexate (>100 mg/m ²)	
Minimal (emesis risk, <10% without antiemetics)	
Bleomycin	α-, β-, γ-interferon
Bevacizumab	Melphalan
Busulfan	Mercaptopurine
Chlorambucil	Methotrexate (<100 mg/m ²)
Cladribine	Thioguanine
Cytarabine (<100 mg/m ²)	Vinblastine
Fludarabine	Vincristine
Hormone	Vinorelbine
Hydroxyurea	

particular, the emetogenic potential of oral chemotherapeutic agents is recognized separately (Table 2). In the revised classifications (MASCC and NCCN), i.v. etoposide is labeled as having low emetogenic potential. However, oral etoposide is classified as having moderate emetogenic potential, implying that there is a 30%–90% incidence of eme-

Table 2. Emetogenic risk of oral chemotherapeutic agents [5, 6]

High (emesis risk, >90% without antiemetics)	
Hexamethylmelamine	Procarbazine
Moderate (emesis risk, 30%–90% without antiemetics)	
Cyclophosphamide	Temozolomide
Etoposide	Vinorelbine
Imatinib	
Low (emesis risk, 10%–30% without antiemetics)	
Capecitabine	Fludarabine
Minimal (emesis risk, <10% without antiemetics)	
Chlorambucil	Melphalan
Erlotinib	Methotrexate
Gefitinib	Sorafenib
Hydroxyurea	Sunitinib
L-Phenylalanine mustard	6-Thioguanine

sis [5, 6]. In a recently published study by Einhorn et al. [9], oral etoposide seemed indeed to have only low emetogenic potential. Also of interest is that imatinib is classified by the MASCC and NCCN guidelines as a moderately emetogenic agent, whereas the daily use of antiemetics is not recommended in the special case of imatinib by the NCCN. The ASCO guidelines do not implicate any of the oral chemotherapeutic agents in their classification system [4].

PATIENT-RELATED RISK FACTORS

Patient-related risk factors, including young age, female gender, a history of low alcohol intake, experience of emesis during pregnancy, impaired quality of life, and previous experience with chemotherapy, are known to increase the risk for CINV [4–6, 10, 11]. In the choice of the optimal antiemetic prophylaxis, patient-related risk factors have no influence on the primary decision. Further research is necessary to verify the usefulness of integrating a patient-related risk factor profile into the primary decision-making process. This would make sense, considering the wide range of emetogenic potential (30%–90%) in the moderately emetogenic setting. However, whether or not such a model would translate into daily routine practice is questionable.

ANTIEMETICS

5-HT₃RAs

The 5-HT₃RAs are without doubt the most effective antiemetics in the prophylaxis of acute CINV. The different 5-HT₃RAs

appear to be interchangeable. The lowest fully effective once-daily dose for each agent should be used as indicated in Table 3. The oral and i.v. routes are similarly effective. These statements are supported by all three guidelines.

Dolasetron

All three guidelines recommend the same doses of dolasetron of 100 mg or 1.8 mg/kg i.v. and 100 mg orally.

Granisetron

All three guidelines recommend granisetron at a dose of 1 mg or 0.01 mg/kg i.v., and 2 mg orally (MASCC and ASCO) or 1–2 mg orally (NCCN).

Ondansetron

In regard to the dosing of ondansetron, different statements are given by the NCCN than by the MASCC and ASCO. As such, the NCCN guidelines recommend ondansetron at a dose of 16–24 mg orally and 8–12 mg (maximum, 32 mg) i.v., whereas the MASCC and ASCO guidelines recommend ondansetron at a dose of 24 mg orally (MASCC, 16 mg orally for moderately emetogenic chemotherapy) and 8 mg or 0.15 mg/kg i.v. In a recently published meta-analysis comparing low-dose ondansetron (8 mg) with high-dose ondansetron (24 or 32 mg), in a subanalysis in cisplatin-based chemotherapy, high-dose ondansetron appeared to be more effective ($p = .012$) [12].

Palonosetron

All three guidelines recommend palonosetron at a dose of 0.25 mg i.v. Oral palonosetron is not yet available. Palonosetron has a significantly longer half-life and a higher binding activity than the other 5-HT₃RAs. The actual role of palonosetron in comparison with the other available 5-HT₃RAs is discussed controversially in the guidelines. However, none of the three guidelines designates a preferred 5-HT₃RA, although palonosetron outperformed ondansetron and dolasetron in some secondary endpoints in one study [13]. For a better understanding, the results of the three available randomized studies with palonosetron in the acute phase are outlined in Table 4. In a recently published meta-analysis, palonosetron was not included because only two studies were fully published at that time [12–14].

Tropisetron

A dose of 5 mg orally or i.v. is recommended for tropisetron by the ASCO and MASCC guidelines, whereas tropisetron is not part of the NCCN guidelines because it is not available in the U.S.

Table 3. Recommended doses of antiemetics [4–6]

Agent	Route	Recommended dose (once daily)
5-HT ₃ -receptor antagonist		
Ondansetron	Oral	24 mg (high), 16 mg (moderate) ^a
	i.v.	8 mg (0.15 mg/kg)
Granisetron	Oral	2 mg
	i.v.	1 mg (0.01 mg/kg)
Tropisetron	Oral	5 mg
	i.v.	5 mg
Dolasetron	Oral	100 mg
	i.v.	100 mg (1.8 mg/kg)
Palonosetron	i.v.	0.25 mg
Steroids		
Dexamethasone	Oral/i.v.	12 mg (highly emetogenic, with aprepitant), 20 mg without aprepitant; 8 mg (moderately emetogenic); 8 mg (high/moderate) days 2 and 3
NK ₁ -receptor antagonist		
Aprepitant	Oral	125 mg on day 1, 80 mg on days 2 and 3

^a8 mg twice daily is recommended.

Table 4. Palonosetron versus ondansetron and dolasetron: details of cisplatin-based and non-cisplatin-based studies and efficacy results; acute emesis

Chemotherapy	Study	n of patients	Dose (mg/day)			Acute complete response (%)			p-value
			Palonosetron	Ondansetron	Dolasetron	Control	Palonosetron	Comparator	
Cisplatin based	Aapro et al. (2006) [30]	667	0.25, 0.75	32		Blind	59.2, 65.5	57.0	NS
Not cisplatin based	Gralla et al. (2003) [14]	563	0.25, 0.75	32		Blind	81.0, 73.5	68.8	.0085
	Eisenberg et al. (2003) [13]	569	0.25, 0.75		100	Blind	63.0, 57.1	52.9	.049

Abbreviation: NS, not significant.

Steroids, Dexamethasone

Although not approved as an antiemetic, dexamethasone plays a major role in the prevention of acute and delayed CINV and is an integral component of almost all antiemetic regimens [15, 16]. All three guidelines recommend the use of dexamethasone for the acute prevention of highly, moderately, and low emetogenic chemotherapy. For the prevention of delayed emesis, dexamethasone is recommended *in combination* with aprepitant for highly emetogenic chemotherapy (MASCC, ASCO, NCCN), but not for moderately emetogenic chemotherapy (MASCC, ASCO). Only the NCCN guidelines suggest dexamethasone as a possible combination partner for aprepitant with moderately emetogenic chemotherapy. This recommendation of the MASCC and ASCO expert panel is mostly driven by the study of Warr et al. [17]

in patients receiving moderately emetogenic chemotherapy. In that study, aprepitant was given as monotherapy for the prevention of delayed CINV. A complete response rate of 55%, in comparison with 49% for ondansetron, was achieved in the delayed phase. This result might suggest that the combination of dexamethasone and aprepitant in the delayed phase would have greater antiemetic efficacy. This might be the reason for the NCCN panel recommending this combination in the moderately emetogenic setting in the delayed phase. Further studies are warranted to clarify this clinically important question.

When combined with aprepitant, dose reduction of dexamethasone (dexamethasone is a sensitive substrate of the cytochrome P450 [CYP] 3A4 enzyme) has to be undertaken. For the prevention of acute CINV, the dose of choice should be 20

mg of dexamethasone (12 mg when coadministered with aprepitant) for highly emetogenic chemotherapy and a single 8-mg dose of dexamethasone (12 mg in the NCCN guidelines) for moderately emetogenic chemotherapy (Table 3). These dose recommendations are largely driven by studies from the Italian Group for Antiemetic Research [18, 19].

NK₁RAs, Aprepitant

Aprepitant is the first representative of this new group that blocks the NK₁ receptor in the brainstem emetic center and gastrointestinal tract [20]. So far, it is only available for oral use and should be administered as indicated in Table 3, as recommended by all three guidelines. Published studies have demonstrated that the addition of an NK₁RA to standard antiemetic therapy (5-HT₃RA plus dexamethasone) appears to have a significant effect in controlling cisplatin-induced acute as well as delayed emesis. In all studies, the comparative benefit of the aprepitant regimen was more pronounced in the delayed phase [20–22]. The use of aprepitant is unanimously suggested by all three guidelines for highly emetogenic chemotherapy and, in part, for moderately emetogenic chemotherapy. In the moderately emetogenic setting, one study has been published so far, which formed the basis for the recommendation of aprepitant for anthracycline and cyclophosphamide–based emetogenic chemotherapy [17]. In that study, by Warr et al. [17], the triple combination of ondansetron, dexamethasone, and aprepitant used in the first 24 hours, followed by aprepitant monotherapy for another 2 days, proved to be superior over the whole 5-day study period (51% versus 42%; $p = .015$). However, there was no significant difference in the delayed period (49% versus 55%; $p = .064$). Because only patients receiving an anthracycline and cyclophosphamide–based regimen were included in this study, the MASCC and ASCO guidelines restrict the recommendation of the triple combination in the moderately emetogenic setting to this “high-risk” chemotherapeutic regimen. The NCCN guidelines, however, recommended aprepitant in the moderately emetogenic setting in selected patients based on the emetogenic potential of the chemotherapy.

In the MASCC guidelines, it was noted that no trial so far has compared aprepitant with dexamethasone for delayed emesis with the previous standard of dexamethasone combined with a 5-HT₃RA in highly emetogenic chemotherapy [5]. In the meantime, a study that addressed this question was published by Schmoll et al. [22] and showed that aprepitant combined with dexamethasone was superior to ondansetron and dexamethasone in the delayed phase.

Aprepitant is a moderate inhibitor of CYP3A4; therefore, the dexamethasone dose has to be reduced, as discussed before. Theoretical concerns that aprepitant might

interact with chemotherapeutic agents could not be demonstrated in preclinical and clinical studies so far [23].

Metoclopramide

Metoclopramide was part of the former MASCC, ASCO, and NCCN guidelines and was suggested for the prevention of delayed emesis [2, 3]. Although metoclopramide was proven to be as effective as 5-HT₃RAs when combined with steroids in the prevention of delayed CINV [24, 25], it was not recommended again in the new guidelines in this setting. It was stated that metoclopramide should be reserved for special circumstances, including known intolerance to 5-HT₃RAs or steroids. However, because 5-HT₃RAs are recommended as an alternative to dexamethasone in the delayed phase for moderately emetogenic chemotherapy, metoclopramide might also be an adequate alternative, although not recommended by the guidelines. A meta-analysis comparing the 5-HT₃RAs with metoclopramide in the delayed phase for moderately emetogenic chemotherapy would be beneficial.

Cannabinoids

The combination of weak antiemetic efficacy with potentially beneficial side effects (sedation, euphoria) makes cannabinoids a useful adjunct to modern antiemetic therapy in selected patients. However, the associated side effects of dizziness and dysphoria should not be underestimated. In the ASCO and NCCN guidelines, cannabinoids are advised in patients intolerant or refractory to 5-HT₃RAs or steroids and aprepitant. Interestingly, in a systematic review of the efficacy of oral cannabinoids in the prevention of nausea and vomiting, it was found that cannabinoids were slightly better than conventional antiemetics (e.g., metoclopramide, phenothiazines, haloperidol). However, their usefulness was generally limited by the high incidence of toxic effects, such as dizziness, dysphoria, and hallucinations.

PREVENTION OF CINV

Highly Emetogenic Chemotherapy

Acute CINV

All three guidelines unanimously suggest a combination of a 5-HT₃RA, dexamethasone, and aprepitant within the first 24 hours for acute CINV with highly emetogenic chemotherapy (Table 5).

Delayed CINV

Trials have indicated that from 60% to nearly 90% of patients receiving cisplatin will experience delayed emesis if not given preventive antiemetics. Therefore, appropri-

Table 5. Antiemetic prevention based on emesis risk category (MASCC, ASCO, NCCN) [4–6]

Group	Recommendation							
	High		Moderate		Low	Minimal		
	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV
MASCC	5-HT ₃ RA + dexamethasone + aprepitant	Dexamethasone + aprepitant	1. Anthracycline/cyclophosphamide 5-HT ₃ RA + dexamethasone + aprepitant 2. Other than anthracycline/cyclophosphamide 5-HT ₃ RA + dexamethasone	Aprepitant or dexamethasone Dexamethasone, 5-HT ₃ RA may be used as an alternative	Dexamethasone	^a	^a	^a
ASCO	5-HT ₃ RA + dexamethasone + aprepitant	Dexamethasone + aprepitant	1. Anthracycline/cyclophosphamide 5-HT ₃ RA + dexamethasone + aprepitant 2. Other than anthracycline/cyclophosphamide 5-HT ₃ RA + dexamethasone	Aprepitant Dexamethasone or a 5-HT ₃ RA	Dexamethasone	^a	^a	^a
NCCN	5-HT ₃ RA + dexamethasone + aprepitant ± lorazepam	Dexamethasone + aprepitant ± lorazepam	1. Anthracycline/cyclophosphamide or in selected patients 5-HT ₃ RA + dexamethasone + aprepitant ± lorazepam 2. Other than anthracycline/cyclophosphamide 5-HT ₃ RA + dexamethasone ± lorazepam	Aprepitant ± dexamethasone ± lorazepam Dexamethasone or 5-HT ₃ RA, both ± lorazepam	Dexamethasone ± Lorazepam or Prochlorperazine ± lorazepam or metoclopramide ± lorazepam or	^a	^a	^a

^aNo routine prophylaxis.
Abbreviations: 5-HT₃RA, 5-HT₃-receptor antagonist; ASCO, American Society of Clinical Oncology; CINV, chemotherapy-induced nausea and vomiting; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network.

ate prophylaxis is indispensable. All three guidelines suggest the combination of dexamethasone and aprepitant for delayed CINV with highly emetogenic chemotherapy.

Moderately Emetogenic Chemotherapy

Acute CINV

All three guidelines recommend the combination of a 5-HT₃RA plus dexamethasone with or without aprepitant for acute CINV with moderately emetogenic chemotherapy. However, the key question in this setting is whether aprepitant should be part of the antiemetic prophylaxis. The ASCO and MASCC guidelines recommend the triple combination (a 5-HT₃RA, dexamethasone, and aprepitant) for patients receiving the combination of an anthra-

cycline and cyclophosphamide-based regimen. The NCCN guidelines, however, broaden the spectrum of the use of aprepitant in this setting and advise use in selected patients receiving other chemotherapies of moderately emetogenic risk (e.g., carboplatin, epirubicin, ifosfamide, irinotecan).

Delayed CINV

Dexamethasone is the preferred agent to use for delayed CINV with moderately emetogenic chemotherapy. Nonetheless, when aprepitant is used for the prevention of acute CINV then it should also be used for the prophylaxis of delayed CINV as monotherapy, as stated by the MASCC and ASCO guidelines. As discussed before, the NCCN guidelines suggest aprepitant with or without dexamethasone in this situation. A 5-HT₃RA can be used as an alternative, although their therapeutic role in

the delayed phase is rather limited [26]. In contrast to all three previously published guidelines, metoclopramide is not reflected in the new guidelines as an alternative option (see above).

Low Emetogenic Chemotherapy

The MASCC and ASCO guidelines unanimously recommend the use of a steroid alone in the first 24 hours and no prophylaxis beyond 24 hours for acute CINV with low emetogenic chemotherapy. The NCCN guidelines recommend prochlorperazine or metoclopramide as well, as alternative drugs to dexamethasone.

Minimally Emetogenic Chemotherapy

All three guidelines suggest that, for patients treated with agents of low emetic risk, no antiemetic drug should be routinely administered before chemotherapy.

MANAGEMENT OF BREAKTHROUGH AND REFRACTORY CINV

Breakthrough CINV is defined as an event that happens in spite of optimal preventive treatment. Refractory CINV is CINV that recurs in subsequent cycles of therapy when all previous preventive and rescue treatments fail. If optimal treatment has been given as prophylaxis, repeated dosing of the same agents is unlikely to be successful; the addition of dopamine-receptor antagonists (metoclopramide) might be useful, or adding other agents such as benzodiazepines or neuroleptics. Olanzapine, an atypical neuroleptic, could also be considered, as suggested by the MASCC and NCCN guidelines. The role of palonosetron, a new 5-HT₃RA, has not yet been defined in this setting [5].

MULTIPLE-DAY CHEMOTHERAPY

For multiple-day cisplatin, the expert panel creating the MASCC guidelines recommended the use of a 5-HT₃RA in combination with dexamethasone for acute CINV and dexamethasone alone for delayed CINV. The use of an NK₁RA remains to be defined, as stated by the MASCC. However, the NCCN guidelines advise the application of aprepitant for at least the first 3 days, in analogy to highly emetogenic chemotherapy. Furthermore, the NCCN guidelines explicitly mention palonosetron in this setting.

OTHER ANTIEMETICS

Benzodiazepines

Benzodiazepines can be a useful addition to antiemetic regimens in certain circumstances, such as anxiety and risk reduction of anticipatory CINV or in patients with refractory and breakthrough emesis, as suggested by all three guidelines.

Antihistamines

Although often administered, studies with diphenhydramine or hydroxyzine in the prevention of CINV have not shown any antiemetic activity [4].

Olanzapine

Olanzapine, an atypical antipsychotic drug, has potential antiemetic properties because of its action at multiple receptor sites implicated in the control of nausea and vomiting [27]. In a phase II trial of olanzapine in combination with granisetron and dexamethasone for the prevention of CINV, the combination therapy proved to be highly effective in controlling acute and delayed CINV in patients receiving highly and moderately emetogenic chemotherapy [28]. In 10 patients receiving highly emetogenic chemotherapy, a complete response (no emesis, no rescue) was achieved in 100% of patients in the first 24 hours, and in 80% of patients on days 2–5. Results for moderately emetogenic chemotherapy were similar. The latest phase II study by Navari et al. [29] showed exceptionally high complete protection rates from both acute and delayed CINV using a combination of palonosetron (day 1), dexamethasone (day 1), and olanzapine (days 1–4) in patients receiving highly or moderately emetogenic chemotherapy. As a consequence, olanzapine is mentioned by the MASCC and NCCN guidelines for the treatment of refractory and breakthrough emesis. A dose of 2.5–5 mg olanzapine is suggested.

CONCLUSION

Treatment guidelines are important because they provide clinicians with a series of recommendations developed from the consensus opinions of international experts based on their interpretation of the most recent clinical trial data. Despite some differences among the MASCC, ASCO, and NCCN guidelines, all provide updated references and recommendations to guide the optimal use of antiemetics. However, the need for more effective practical implementation of treatment guidelines is crucial to improve the quality of care of cancer patients.

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