special article

Applicability of the National Comprehensive Cancer Network/ Multinational Association of Supportive Care in Cancer Guidelines for Prevention and Management of Chemotherapy-Induced Nausea and Vomiting in Southeast Asia: A Consensus Statement

executive summary

A meeting of regional experts was convened in Manila, Philippines, to develop a resource-stratified chemotherapy-induced nausea and vomiting (CINV) management guideline. In patients treated with highly emetogenic chemotherapy in general clinical settings, triple therapy with a serotonin (5-hydroxytryptamine-3 [5-HT$_3$]) antagonist (preferably palonosetron), dexamethasone, and aprepitant is recommended for acute CINV prevention. In resource-restricted settings, triple therapy is still recommended, although a 5-HT$_3$ antagonist other than palonosetron may be used. In both general and resource-restricted settings, dual therapy with dexamethasone (days 2 to 4) and aprepitant (days 2 to 3) is recommended to prevent delayed CINV. In patients treated with moderately emetogenic chemotherapy, dual therapy with a 5-HT$_3$ antagonist, preferably palonosetron, and dexamethasone is recommended for acute CINV prevention in general settings; any 5-HT$_3$ antagonist can be combined with dexamethasone in resource-restricted environments. In general settings, for the prevention of delayed CINV associated with moderately emetogenic chemotherapy, corticosteroid monotherapy on days 2 and 3 is recommended. If aprepitant is used on day 1, it should be continued on days 2 and 3. Prevention of delayed CINV with corticosteroids is preferred in resource-restricted settings. The expert panel also developed CINV management guidelines for anthracycline plus cyclophosphamide combination schedules, multiday cisplatin, and chemotherapy with low or minimal emetogenic potential, and its recommendations are detailed in this review. Overall, these regional guidelines provide definitive guidance for CINV management in general and resource-restricted settings. These consensus recommendations are anticipated to contribute to collaborative efforts to improve CINV management in Southeast Asia.

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is one of the most troublesome adverse effects of cancer treatment, with a significant negative impact on quality of life.[1-3] Several new treatments for CINV have been introduced and are now recommended in evidence-based antiemetic guidelines developed by ASCO,[4] the European Society of Medical Oncology (ESMO) and Multinational Association of Supportive Care in Cancer (MASCC),[5] and the National Comprehensive Cancer Network (NCCN).[6] Although guideline-recommended therapies significantly reduce the risk of CINV, such regimens often are underused in CINV prevention.[7]

Until recently, little has been documented about the prevalence and management of CINV in the Asia-Pacific region or the applicability of international CINV management guidelines to Asian populations. International guidelines are mostly based on studies conducted in white patients, but ethnic differences and genetic polymorphisms may contribute to CINV and affect the utility of antiemetic treatment.[3,8-11]

To optimize prevention and management of CINV in Asian patients, regional guidelines should take into account ethnic variations in CINV risk as well as differences in health care systems, clinical practice, and treatment availability and affordability. A meeting of experts from Malaysia, the Philippines, and Singapore was convened in Manila, Philippines, on November 24, 2014, to assess the local applicability of international CINV management guidelines and to develop regionally appropriate modifications. Principal considerations were current clinical practice, treatment availability and affordability, and specifics of local health care systems. This article describes consensus-based outcomes from the discussions at the Manila meeting.

DISCUSSION

Burden of CINV in Asia

Several publications provide insight into CINV characteristics and treatment in the Asia-Pacific region.[12-17] Observational studies in Malaysia, the Philippines, and Singapore indicate that nausea occurs more frequently than vomiting (Table 1). However, the definitions for nausea and vomiting vary among studies, which makes comparison of the incidence difficult.

The following risk factors for CINV are the same in Southeast Asia as in Europe:

- Type of chemotherapy administered. In a study conducted among patients with head and neck cancer in Singapore, single-day rather than multiday cisplatin therapy was associated with a 1.5-fold increase in the risk of nausea.[12]
- CINV experienced during previous chemotherapy.[12,14,18] In a multinational, prospective, observational study in patients who received highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC), previous CINV was a significant predictor of subsequent vomiting and clinically significant nausea and/or vomiting.[18]

Table 1. Incidence of Chemotherapy-Induced Nausea and Vomiting of Any Grade Reported in Malaysia, the Philippines, and Singapore

First Author	Country	No. of Patients	Chemotherapy Schedule	Nausea (%)	Vomiting (%)
Chan[13]	Malaysia	99	PC: 36.7% of patients GEM: 16.7% of patients DOX: 13.3% of patients	83.3	78.9
Williams[15]	Philippines	63	ALK, ANT, VIN, other*	73.0	52.4
Chan[12]	Singapore	235	IV CIS on day 1 of a 7-day (40 mg/m^2) or 21-day (100 mg/m^2) cycle	73.7	24.7
			IV CIS 20 mg/m^2/d and IV FU 1,000 mg/m^2/d on days 1, 2, 3, and 4 of a 28-day cycle	48.9	28.9
Shih[14]	Singapore	91	IV DOX 60 mg/m^2 + CYC 600 mg/m^2 every 14 or 21 days for up to five cycles	25.3†	68.1†
Yap[16]	Singapore	710	IV DOX 60 mg/m^2/d + CYC 600 mg/m^2/d, or IV DOX 50 mg/m^2/d + CYC 500 mg/m^2/d + FU 500 mg/m^2/d, or IV EPI 75-100 mg/m^2/d + CYC 500 mg/m^2/d + FU 500 mg/m^2/d, or IV OXA 130 mg/m^2/d + oral CAP 2,000 mg/m^2/d, or IV CIS 20-100 mg/m^2/d ± FU 1,000 mg/m^2/d	55.0† 67.0‡	15.0† 22.0‡
Chan[17]	Singapore	156	CAP days 1-14 (median, 1,775 mg/m^2/d) + OXA day 1 (median, 104 mg/m^2) every 21 days	35.3† 46.8‡	6.4† 14.7‡

Abbreviations: ALK, alkylating agents (chlorambucil, cyclophosphamide, fluorouracil, thiotepa, busulfan); ANT, antimetabolites (fluorouracil, capecitabine, mercaptopurine, methotrexate, gemcitabine, cytarabine, fludarabine); CAP, capecitabine; CIS, cisplatin; CYC, cyclophosphamide; DOX, doxorubicin; EPI, epirubicin; FU, fluorouracil; GEM, gemcitabine; IV, intravenous; OXA, oxaliplatin; PC, paclitaxel + carboplatin; VIN, vinca alkaloids (vinblastine, vincristine, vinorelbine).

*No indication given of proportion of patients who receive each chemotherapy.

†Acute nausea or vomiting.

‡Delayed nausea or vomiting.

- Nonadherence to antiemetic therapy. In a large, prospective study of patients with breast cancer who received anthracycline-based chemotherapy in Singapore, nonadherent patients were less likely to achieve complete CINV control than adherent patients ($P = .048$).[19]
- Anxiety and history of motion sickness. A study of patients who received doxorubicin and cyclophosphamide for breast cancer found that anxiety predicted development of acute ($P = .004$) and delayed nausea ($P = .024$) and that a history of motion sickness predicted delayed vomiting ($P = .047$).[14]
- Concomitant radiotherapy and poor performance status. Among 235 patients treated with cisplatin-based regimens for head and neck cancer, concomitant radiotherapy was associated with nausea ($P = .022$), and patients with an Eastern Cooperative Oncology Group score ≥ 1 were 2.4 times more likely to experience vomiting ($P = .046$) than patients with a score of 0.[12]
- Female sex and younger than 50 years of age. The Pan Australasia Chemotherapy-Induced Emesis (PrACTICE) study conducted in Asian countries evaluated 648 patients who received HEC or MEC. Female versus male patients were less likely to have a complete response (no vomiting or use of rescue antiemetic therapy) during chemotherapy cycles two and three ($P < .001$). Patients younger than 50 years of age were more likely ($P \leq .004$) to experience CINV in cycles two and three than older patients.[18]
- Cancer-related fatigue. Poon et al[20] evaluated cancer-related fatigue scores in 473 patients with GI or breast cancers. Patients with lower versus higher fatigue interference scores were more likely to have a complete response to antiemetics (odds ratio, 1.57; $P = .027$).[20]
- Genetic polymorphisms in the *ABCB1* transporter gene. Particular haplotypes of the *ABCB1* gene are associated with an increased risk of CINV.[9-11] In Indonesia, the CTG haplotype is associated with an increased risk of delayed CINV in patients who receive HEC.[10] Similarly, the *ABCB1* CG haplotype is associated with an increased risk of acute CINV in Chinese patients during high-dose cytarabine for acute myeloid leukemia,[11] and the 3435C>T polymorphism is a risk factor for acute CINV in Japanese women who receive chemotherapy for breast cancer.[9]

Low rates of alcohol use have been reported in Asian patients with cancer,[21,22] and a history of low alcohol consumption has been linked with chemotherapy-induced emesis.[23] However, knowledge is limited about the impact of alcohol use on CINV in daily clinical practice.[24]

Antiemetic Therapy: Use of Guidelines and Prescribing Patterns in Asia

The clinical management of CINV in the Asia-Pacific has been investigated as part of the PrACTICE study, a prospective, observational study conducted in Australia, China, India, Singapore, South Korea, and Taiwan.[25] In PrACTICE, 84% of physicians regularly used antiemetic guidelines, with NCCN guidelines consulted by 65% of physicians, and MASCC/ESMO guidelines by 39%.[26] Almost all physicians (97%) considered guidelines to be useful for CINV management.[26]

A high rate of serotonin (5-hydroxytryptamine-3 [5-HT_3]) antagonist use (96% to 97%) is evident in patients who receive HEC or MEC, but the prescribing of other antiemetic therapies varies markedly among countries.[26] Among patients who have received HEC, 95% in Australia also received corticosteroids, but only 70% in China did; corresponding rates of neurokinin-1 (NK_1) antagonist use were 91% and 0%, respectively. NK_1 antagonist prescribing was probably affected by international differences in drug availability and reimbursement, whereas reasons for underuse of corticosteroids are less clear.[26]

The PrACTICE study showed that corticosteroids generally are underprescribed in Asian patients, particularly in the delayed phase after HEC and MEC.[26] Some prescribers may not be aware of the guideline recommendations for corticosteroids, have concerns about the potential adverse effects of administering corticosteroids for 3 to 4 days, and/or lack confidence in these drugs' antiemetic efficacy.[26] Underuse of corticosteroids may also be partly related to cultural perceptions and corticosteroid aversion in Asian patients.[19,26,27] Dexamethasone is inexpensive, so to overcome barriers to its use would improve CINV prophylaxis without significant additional treatment costs.[26] Asia-specific CINV management recommendations may help to overcome barriers to corticosteroid use and support rational use of NK_1 antagonists as they become more readily available.

Consensus Development Process

The Manila panel discussed NCCN[6] and MASCC/ESMO[5] recommendations and their applicability

to Southeast Asia. These guidelines were selected because they are the most widely used in the region.[26] For each recommendation, the panel voted on the level of confidence and level of consensus. Level of confidence (high, moderate, or low) was based on the panel's assessment of the strength of the published evidence to support that recommendation. Consensus was defined as high for seven votes, moderate for five or six votes, and low for three or four votes. The panel also developed specific recommendations for resource-limited settings so that guidance could be provided for oncologists who practice in areas with limited access to newer and/or more costly antiemetics.

Resource-restricted settings were defined as having the capacity to offer basic core antiemetic therapy and any other antiemetic drugs that are attainable with restricted financial means and basic infrastructure. Higher-level resource settings were defined as having the capacity to offer important antiemetic therapy that would be difficult to attain and would not be standard therapy in a resource-restricted setting but that may be recommended in international guidelines regardless of resource constraints.

Since the Manila meeting in 2014, the MASCC guidelines have been updated.[28] Therefore, the updated MASCC guidelines have been reviewed, and an additional literature search of PubMed was conducted in July 2016 that used the search term CINV to identify any other relevant evidence, with a focus on studies conducted in the Asia-Pacific.

The consensus reached in 2014 remains essentially unchanged except where indicated. Several agents added to the 2016 MASCC/ESMO guidelines[28] (rolapitant, netupitant plus palonosetron combination) were not available in the Asia-Pacific at the time this article was submitted.

SUMMARY

Emetogenic Chemotherapies

NCCN[6] and MASCC/ESMO[5] guidelines both stratified recommendations according to the emetogenic potential of chemotherapies. The Manila panel agrees with the NCCN classification of HEC or MEC intravenous agents,[6] with some modifications (Table 2).

The panel recommends that cisplatin dosages > 50 mg/m^2 be included in the HEC classification (high confidence; high consensus), whereas NCCN and MASCC/ESMO guidelines characterize cisplatin as highly emetogenic, irrespective of dosage.[5,6,28] Although cisplatin generally is administered at a dosage of > 50 mg/m^2, lower dosages sometimes are used (eg, in combination with radiotherapy). Because evidence of a dose-related effect of cisplatin on CINV exists,[12] the panel defines appropriate CINV management recommendations for patients who receive cisplatin < 50 mg/m^2.

The panel also advocates a separate classification for anthracycline plus cyclophosphamide (AC) combination regimens (high confidence; high consensus). Both the NCCN and 2016 MASCC/ESMO guidelines classify AC combinations as HEC.[6,28] The earlier MASCC/ESMO recommendations classified anthracyclines as MEC, irrespective of dosage, and cyclophosphamide as HEC (at dosages $\geq 1{,}500$ mg/m^2) or MEC ($< 1{,}500$ mg/m^2).[28]

Daunorubicin and idarubicin are listed as MECs, regardless of dosage, in the NCCN guidelines,[6] whereas doxorubicin and epirubicin are documented as HEC or MEC, which depends on dosage. NCCN also acknowledges that some anthracyclines (daunorubicin, doxorubicin, epirubicin) may be highly emetogenic in some patients; cyclophosphamide alone is categorized as HEC at dosages $> 1{,}500$ mg/m^2 or MEC at doses $\leq 1{,}500$ mg/m^2.[6]

The panel recommends that AC combinations be labeled as a separate emetogenic category. Such categorization permits specific antiemetic treatment recommendations to be made, which closely reflect regional clinical practice (see the section on antiemetic prophylaxis in patients who receive AC).

The panel concurs with the following NCCN categories for other emesis risk groups (low confidence; high consensus): intravenous agents with low or minimal emetogenicity and oral agents with minimal to low or moderate to high emetic risk[6] (Table 2). The emetogenic risk for oral antineoplastic agents is largely based on consensus and data from registration trials in which patients often received antiemetic prophylaxis.[5] Oncologists should therefore be aware of the low level of confidence in emetogenic classification for newer antineoplastics, particularly oral agents.

Antiemetic Prophylaxis

The Manila panel developed recommendations for antiemetic use in the prevention and treatment of acute and delayed CINV in patients who receive various types of chemotherapy in general and resource-restricted settings (Table 3). With regard to resource stratification, treatment choice is driven not only by drug acquisition cost but also

Table 2. Manila Expert Panel Classification of Intravenous Agents With Moderate to High Emetogenicity

High Risk*	Special Case	Moderate Risk†
Carmustine (> 250 mg/m^2)	Anthracycline + cyclophosphamide combinations	Aldesleukin (> 12-15 million IU/m^2)
Cisplatin (> 50 mg/m^2)		Amifostine (> 300 mg/m^2)
Cyclophosphamide (> 1,500 mg/m^2)		Arsenic trioxide
Dacarbazine		Azacitadine
Doxorubicin (⩾ 60 mg/m^2)		Bendamustine
Epirubicin (> 90 mg/m^2)		Busulfan
Ifosfamide (⩽ 2 g/m^2/dose)		Carboplatin‡
Mechlorethamine		Carmustine (⩽ 250 mg/m^2)
Streptozocin		Cisplatin (⩽ 50 mg/m^2)
		Clofarabine
		Cyclophosphamide (⩽ 1,500 mg/m^2)
		Cytarabine (> 200 mg/m^2)
		Dactinomycin‡
		Daunorubicin‡
		Doxorubicin‡ (< 60 mg/m^2)
		Epirubicin‡ (⩽ 90 mg/m^2)
		Idarubicin
		Ifosfamide‡ (⩽ 2 g/m^2/dose)
		Interferon alfa (⩽ 10 million IU/m^2)
		Irinotecan‡
		Melphalan
		Methotrexate‡ (⩾ 250 mg/m^2)
		Oxaliplatin
		Temozolomide

Abbreviation: IU, International Unit.
*Emesis frequency > 90%.
†Emesis frequency 30% to 90%.
‡May be highly emetogenic in some patients.

by factors such as the overall cost-effectiveness of antiemetic schedules, the potential for longer hospital stays as a result of complications, patient loss of income, patient willingness to pay, unexpected hospital visits to control CINV between cycles, and potentially increased costs to families if the patient needs additional care.

Patients Who Receive HEC

Acute CINV. In most clinical settings, the panel suggests triple therapy with a 5-HT$_3$ antagonist (preferably palonosetron), dexamethasone, and aprepitant (high confidence; high consensus). Support for this recommendation stems from data from randomized, double-blind studies (including one in Chinese patients) in which a 5-HT$_3$ antagonist plus dexamethasone and aprepitant was superior to a 5-HT$_3$ antagonist plus dexamethasone in completely controlling CINV in patients treated with HEC.[29,30] In a trial in 411 Asian patients, the complete response rate was significantly greater with triple versus dual therapy during the overall phase (0 to 120 hours after initiation of HEC; 69.6% *v*57.0%; $P = .007$) and the delayed phase (25 to 120 hours after initiation of HEC; 74.0% *v*59.4%; $P < .001$).[30] In contrast to a study in non-Asian patients, complete response rates during the acute phase (0 to 24 hours after initiation of HEC) were not significantly different for triple versus dual therapy (79% for both regimens). The relatively high acute phase complete response rate observed in Asian patients treated with dual therapy may have concealed the advantage of triple therapy observed in non-Asian patients.[29,30]

Palonosetron is the recommended 5-HT$_3$ antagonist. A meta-analysis of five randomized studies in 2,057 patients showed that those treated with palonosetron rather than dolasetron, granisetron, or ondansetron had a significantly reduced relative risk of acute nausea (–14%; $P = .007$), delayed nausea (–18%; $P < .001$), acute vomiting (–24%; $P < .001$), and delayed vomiting (–24%; $P < .001$).[31] In addition, palonosetron has a stronger binding affinity at 5-HT$_3$ receptors and a longer half-life (approximately 40 hours) than other 5-HT$_3$ antagonists.[32] These findings explain the clinical rationale for palonosetron to prevent acute and delayed CINV.

The recommended dosage of aprepitant in Southeast Asia is 125 mg orally 1 hour before chemotherapy.[33] NCCN guidelines list either aprepitant or fosaprepitant as appropriate NK$_1$ antagonists for use in triple therapy schedules.[6] The 2016 MASCC/ESMO guidelines recommend aprepitant, fosaprepitant, rolapitant, or netupitant (available in combination with palonosetron),[28] but the latter two agents are not yet available in the Asia-Pacific.

In resource-restricted settings, triple therapy is still recommended, although it is more expensive than dual therapy. Data from Asia, including Singapore, show that the additional acquisition cost of aprepitant is largely offset by reduced rescue medication use, hospitalization, and overall patient management costs.[34,35] However, if the acquisition cost of aprepitant precludes its use as part of a triple therapy regimen in resource-limited

Table 3. Consensus-Based Recommendations for the Use of Antiemetic Agents in Southeast Asia

CINV Type	Setting	Recommendation	Level of Confidence	Level of Consensus
Patients treated with HEC				
Acute	General	Triple therapy with PAL + DEX + APR 125 mg	High	High
	Resource limited	Triple therapy with 5-HT_3 + DEX + APR 125 mg or 5-HT_3 + DEX + OLZ*	High	High
Delayed	General and resource limited	DEX 8 mg on days 2-4 and APR 80 mg on days 2-3	High	High
Patients treated with MEC				
Acute	General	5-HT_3 antagonist (PAL preferred) + DEX ± APR 125 mg†	Moderate	High
	Resource limited	5-HT_3 antagonist + DEX or 5-HT_3 + DEX + OLZ*	High	High
Delayed	General	DEX 8 mg on days 2-3 ± APR 80 mg on days 2-3 (if APR used on day 1)	High	High
	Resource limited	DEX 8 mg on days 2-3	High	High
Patients treated with AC combinations				
Acute	General	5-HT_3 antagonist (PAL preferred) + DEX ± APR 125 mg	Moderate	High
	Resource limited	5-HT_3 antagonist + DEX ± APR 125 mg or 5-HT_3 antagonist + DEX + OLZ	Moderate	High
Delayed	General	DEX 8 mg on days 2-4 ± APR 80 mg on days 2-3 (if APR used on day 1)	High	High
	Resource limited	DEX 8 mg on days 2-4 ± APR 80 mg on days 2-3 (if APR used on day 1) or DEX + OLZ or 5-HT_3 antagonist (PAL preferred) + DEX on day 1 (corticosteroid sparing)	High	High
Patients treated with multiday cisplatin				
Acute	General	Triple therapy with PAL + DEX + APR 125 mg	Moderate	Moderate
	Resource limited	Triple therapy with 5-HT_3 antagonist + DEX ± APR 125 mg or 5-HT_3 antagonist + DEX + OLZ	Moderate	Moderate
Delayed	General and resource limited	DEX ± APR 80 mg on days 2-3 (if APR used on day 1)	Moderate	High
Chemotherapy with low emetogenic risk				
Acute	General and resource limited	5-HT_3 antagonist or DEX or DRA if antiemetics considered appropriate	Low	High
Delayed	General and resource limited	No routine prophylaxis	High	High
Chemotherapy with minimal emetogenic risk				
Acute or delayed	General and resource limited	No routine prophylaxis	High	High

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3; AC, anthracycline + cyclophosphamide; APR, aprepitant; CINV, chemotherapy-induced nausea and vomiting; DEX, dexamethasone; DRA, dopamine receptor antagonist; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; OLZ, olanzapine; PAL, palonosetron.
*Currently, limited data on OLZ efficacy in this setting.
†Patients should receive 5-HT_3 antagonist and DEX in cycle 1, with APR added in subsequent cycles if dual therapy does not achieve CINV control.

settings, olanzapine is an acceptable alternative,[6] although further studies are needed on the role of olanzapine to prevent CINV in patients who receive HEC.

No specific cost-effectiveness data support the use of palonosetron in resource-restricted settings. Thus, another 5-HT_3 antagonist may be used as a triple therapy constituent in patients who receive HEC (high confidence; high consensus). If patients do not respond to one 5-HT_3 antagonist, another with a different metabolic pathway can be tried because genetic polymorphisms in cytochrome P450 (CYP) isoenzymes may lead to interpatient differences in drug metabolism and bioavailability.[36] Table 4 lists the 5-HT_3 antagonists typically used in Southeast Asia.[5,36,37]

Table 4. 5-HT_3 Antagonists and Dosages Typically Used in Southeast Asia

	HEC		MEC	
Agent	**IV**	**Oral**	**IV**	**Oral**
Granisetron	1 mg or 0.01 mg/kg	2 mg	1 mg or 0.01 mg/kg	2 mg
Ondansetron	8 mg or 0.15 mg/kg	24 mg	8 mg or 0.15 mg/kg	16 mg (or 8 mg twice daily)
Palonosetron	0.25 mg	0.5 mg	0.25 mg	0.5 mg
Ramosetron	300 μg*	100 μg	300 μg*	100 μg
Tropisetron	5 mg	5 mg	5 mg	5 mg

Abbreviations: 5-HT3, 5-hydroxytryptamine-3; HEC, highly emetogenic chemotherapy; IV, intravenous; MEC, moderately emetogenic chemotherapy.
*Maximum 600 μg/d.

Delayed CINV. In all clinical settings in Southeast Asia, the panel recommends the use of dual therapy with dexamethasone (days 2 to 4) and aprepitant (days 2 to 3) to prevent delayed CINV (high confidence; high consensus), if resources allow. Clinicians must not use aprepitant on days 2 to 3 if it was not used on day 1 because this is ineffective and wasteful. If aprepitant was not used on day 1, the recommended regimen for preventing delayed CINV is dexamethasone monotherapy.

Typically, 5-HT_3 antagonists are less effective in preventing delayed than acute CINV. A large meta-analysis revealed that the addition of a 5-HT_3 antagonist (dolasetron, granisetron, or ondansetron) to dexamethasone does not significantly improve the antiemetic efficacy of dexamethasone alone.[38] Therefore, use of oral 5-HT_3 antagonists for the prevention of delayed CINV is not recommended.

Although metoclopramide may be a low-cost alternative to aprepitant for delayed CINV prevention,[39] equivalent efficacy has not been demonstrated at doses approved for use in the Asia Pacific, where a maximum metoclopramide dose of 10 mg three times per day is recommended to reduce the risk of neurologic and other dose-related adverse drug reactions.[40]

Patients Who Receive MEC

Acute CINV. The Manila panel recommends dual therapy with a 5-HT_3 antagonist, preferably palonosetron, and dexamethasone in patients treated with MEC in most clinical settings in Southeast Asia (moderate confidence; high consensus). Palonosetron is the preferred 5-HT_3 antagonist because data from multicenter, randomized, double-blind trials have demonstrated superior antiemetic efficacy relative to dolasetron[41] and ondansetron[42] in patients who receive MEC. A meta-analysis of five studies in 2,057 patients treated with HEC or MEC revealed that palonosetron is significantly superior to dolasetron, granisetron, and ondansetron in preventing both acute and delayed CINV.[31] Limited evidence supports adding aprepitant to combination therapy in patients who receive MEC, and the panel recommends that oral aprepitant 125 mg[33] only be added to dual therapy (palonosetron + dexamethasone) in subsequent cycles if CINV is not well controlled by dual therapy in cycle 1; aprepitant should not be used in the first cycle (moderate confidence; high consensus). MECs are not considered emetogenic enough to warrant routine aprepitant use in patients who receive these regimens. In an observational study in Singapore in 156 patients treated with capecitabine plus oxaliplatin (which is moderately emetogenic), 88% had no emesis during dual therapy with a 5-HT_3 antagonist and dexamethasone.[17]

In resource-limited settings, any of the available 5-HT_3 antagonists can be used in combination with dexamethasone to prevent acute CINV in patients treated with MEC, but aprepitant should not because it lacks cost-effectiveness when used with MEC (high confidence; high consensus). Olanzapine is a low-cost alternative to aprepitant if triple therapy is indicated,[6] although further studies are needed on the preventive efficacy of olanzapine in patients who receive MEC.

Delayed CINV. In most clinical settings, the panel recommends monotherapy with a corticosteroid on days 2 and 3 to prevent delayed emesis; if aprepitant is used on day 1, it should be continued on days 2 and 3 (high confidence; high consensus). Corticosteroids, which are inexpensive and effective in preventing delayed CINV, are the preferred treatment in resource-limited settings (high confidence; high consensus); a 5-HT_3 antagonist is a rational alternative for patients who cannot tolerate corticosteroids.

Patients Who Receive AC Combinations

Acute CINV. Patients who receive AC combination therapy should be treated with a 5-HT_3 antagonist (preferably palonosetron) and dexamethasone; oral aprepitant 125 mg can be added in centers without limited resources (moderate confidence; high consensus). In resource-limited centers, the incremental benefit of aprepitant may not justify the cost. An observational study of 91 patients who received AC in Singapore found that most patients tolerated AC chemotherapy moderately well without vomiting.[14] These patients received CINV prophylaxis according to institutional guidelines, which recommended a 5-HT_3 antagonist plus corticosteroid during cycle 1 to prevent acute CINV and a 5-HT_3 antagonist plus corticosteroid plus dopamine antagonist to prevent delayed CINV. Patients who experienced CINV (acute or delayed) during cycle 1 were given concomitant aprepitant during the next cycle, but only nine patients required aprepitant in cycle 2.[14] Thus, aprepitant should not be used routinely to prevent acute CINV in patients treated with AC in Asia (moderate confidence; high consensus), but further studies are required. If triple therapy is considered necessary, an acceptable low-cost option is olanzapine with a 5-HT_3 antagonist and dexamethasone.[6]

Delayed CINV. Typically, corticosteroid dosages used in Southeast Asia (Table 5) are lower than those advocated in international guidelines for CINV management.[5,6] Thus, the panel recommends therapy with dexamethasone 8 mg on days 2 to 3 to prevent delayed emesis in patients treated with AC in most settings. If resources allow, aprepitant 80 mg may be added, with the proviso that aprepitant should be used in the delayed (days 2 to 3) antiemetic schedule only if used previously on day 1 (moderate confidence; high consensus). Alternative strategies in resource-limited settings include an olanzapine-based regimen.[6]

Table 5. Recommended Dexamethasone Dosages for CINV in Southeast Asia

Risk of CINV	Type of CINV	Recommended Dosage
High	Acute	8-16 mg once (12 mg when used with aprepitant)
	Delayed	4-8 mg twice daily for 3-4 days (8 mg once daily when used with aprepitant)
Moderate	Acute	8 mg once
	Delayed	8 mg once daily for 2-3 days
Low	Acute	4-8 mg once

Abbreviation: CINV, chemotherapy-induced nausea and vomiting.

Corticosteroid-sparing regimens may be another option in resource-limited settings. In women who receive AC regimens for breast cancer, a corticosteroid-sparing regimen (single dose of palonosetron then dexamethasone on day 1 only) was no less effective in preventing delayed CINV than continuation of dexamethasone for 3 days.[43]

Patients Who Receive Multiday Cisplatin

Multiday treatment with highly emetogenic schedules presents unique challenges for CINV prevention because patients may experience both acute and delayed CINV, and the risk periods may overlap, depending on the chemotherapy schedules used.[6] Antiemetic therapy, therefore, should be individualized and practical issues considered (eg, administration in the inpatient *v* outpatient setting, preferred route of administration, duration of antiemetic action, tolerability profile, likely patient adherence to treatment).[6] Recommendations from the Manila panel should be regarded as general guidance only.

Acute CINV. In unrestricted resource settings in Southeast Asia, patients treated with multiday cisplatin should receive triple therapy with palonosetron, dexamethasone, and aprepitant to prevent acute CINV. Data that support aprepitant use come from a randomized, placebo-controlled, crossover study in 69 patients with testicular cancer who received a 5-day cisplatin-based schedule.[44] The addition of aprepitant to dexamethasone plus a 5-HT_3 antagonist significantly improved the complete response rate (42% *v* 13% for triple *v* dual therapy, respectively; $P < .001$).[44] However, aprepitant was scheduled over days 3 to 7 of therapy, which differs from the currently approved 3-day dosing regimen of aprepitant. Further studies are required to establish the role and schedule of aprepitant in multiday cisplatin chemotherapy.

In resource-limited environments, an inexpensive 5-HT_3 antagonist should be used instead of palonosetron, and aprepitant should be removed from the triple therapy regimen (moderate confidence; moderate consensus). This recommendation is substantiated by a study conducted by Chan et al[12] in which 45 patients who received multiday (over 5 days) cisplatin received granisetron and dexamethasone (without aprepitant) as antiemetic prophylaxis. Nausea and vomiting were well controlled with 44.4% and 28.9% patients who experienced significant nausea and vomiting, respectively. Triple therapy with olanzapine, a

5-HT_3 antagonist, and dexamethasone is an acceptable and inexpensive alternative.

Delayed CINV. 5-HT_3 antagonists generally are less effective in the management of delayed versus acute CINV.[6,45] Thus, to prevent delayed CINV in patients treated with multiday cisplatin-containing schedules, the panel recommends dexamethasone; aprepitant can be added where resources permit (moderate confidence; high consensus).

Chemotherapy With Low or Minimal Emetogenic Risk

For patients who receive chemotherapy with low emetogenic potential, physicians in the Asia-Pacific should consider the omission of antiemetics to prevent acute CINV. Should antiemetics be considered appropriate, the Manila panel recommends monotherapy with a 5-HT_3 antagonist, dexamethasone, or a dopamine-receptor antagonist (eg, metoclopramide) to prevent acute CINV (low confidence; high consensus); however, limited evidence for this approach exists. Adding a 5-HT_3 antagonist to single-agent therapy with dexamethasone or metoclopramide is not cost-effective in this setting.[46]

No routine prophylaxis is needed to prevent delayed CINV in patients who receive chemotherapy with low emetogenic potential or to prevent acute or delayed CINV in patients who receive chemotherapy with minimal emetogenic potential (high confidence; high consensus). However, these patients should be closely monitored; antiemetic therapy should be administered promptly if CINV occurs.

Table 6. Agents Considered by the Manila Panel as Suitable Treatment for Breakthrough Chemotherapy-Induced Nausea and Vomiting

Agents	Drug
Corticosteroids	Dexamethasone
5-HT_3 antagonists	Dolasetron
	Granisetron
	Ondansetron
	Ramosetron
Atypical antipsychotics	Olanzapine
Short-acting benzodiazepines	Lorazepam
Phenothiazines	Prochlorperazine
	Promethazine
Other	Haloperidol
	Metoclopramide

Anticipatory CINV

Effective control of CINV in the first cycle of chemotherapy is essential because patients who experience CINV during cycle 1 are more likely to have anxiety and anticipatory nausea before subsequent cycles.[47] Patients with anticipatory nausea and vomiting may benefit from behavioral therapies (high confidence; moderate consensus). Benzodiazepines are the only agents that have been shown to reduce the incidence of anticipatory nausea and vomiting, but their efficacy tends to decrease as chemotherapy continues (moderate confidence; low consensus).

Breakthrough/Refractory CINV

Despite the use of recommended prophylaxis, CINV may still develop in some patients. Recommendations for these patients are listed in Table 6. Patients with breakthrough CINV may benefit from switching antiemetic agents (eg, from one 5-HT_3 antagonist to another).[6,48] Evidence supports interracial differences in genetic polymorphisms for CYP enzymes, which may affect the metabolism of various 5-HT_3 antagonists, even between Asian populations.[36] Similarly, polymorphisms in the gene for the ABCB1 efflux transporter may affect the rate at which various 5-HT_3 antagonists cross the blood-brain barrier and, therefore, their antiemetic efficacy.[9-11] This may explain some differences between racial groups or between individuals within the same racial group in the clinical effects of certain 5-HT_3 antagonists.[9-11,36,49] For switching between 5-HT_3 antagonists, it is advisable to choose an agent metabolized by a different CYP enzymatic pathway and to use pharmacogenomic information on the patient's *ABCB1* haplotype, if available.

If a switch is not effective or feasible, the addition of an agent from a different class, such as a dopamine antagonist,[50] olanzapine,[51] benzodiazepine,[6] or phenothiazine, is recommended.[6] Olanzapine has been shown to be more effective than metoclopramide in this setting.[51]

In conclusion, effective CINV management is best achieved by a multidisciplinary team, including oncologists, pharmacists, and nurses.[13,52] Through consultation and collaboration, better prescribing choices can be made for patients with cancer[53] that take into account the emetogenic risk associated with various chemotherapy schedules, specific patient characteristics, and pharmacologic and clinical profiles of antiemetic agents.

The current recommendations for CINV management in Southeast Asia are unique because of

their explicit regional focus and provide guidance for resource-limited centers. The cost-effectiveness of various antiemetic regimens needs to be evaluated to refine these recommendations for resource-limited settings. Meanwhile, the consensus outlined here is anticipated to contribute to improvements in CINV management in Asia.

DOI: https://doi.org/10.1200/JGO.2016.005728
Published online on jgo.org on November 9, 2016.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors

Final approval of manuscript: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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ACKNOWLEDGMENT

We thank MIMS for providing editorial support, collating author feedback, and incorporating revisions. We also acknowledge the important contribution of the late Ahmad Kamal bin Mohamed, MD (MAL), DCO (EDIN), in the conception, planning, and writing of this article.

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Support

Supported by Mundipharma, which provided logistic support and funding for the consensus meeting and paid the authors fair market honoraria for their time spent attending the consensus meeting and discussions. Mundipharma also paid for MIMS to provide writing assistance and editorial support.

REFERENCES

1. Hesketh PJ: Chemotherapy-induced nausea and vomiting. N Engl J Med 358:2482-2494, 2008
2. Martin CG, Rubenstein EB, Elting LS, et al: Measuring chemotherapy-induced nausea and emesis. Cancer 98:645-655, 2003
3. Hassan BA, Yusoff ZB: Negative impact of chemotherapy on breast cancer patients QOL - utility of antiemetic treatment guidelines and the role of race. Asian Pac J Cancer Prev 11:1523-1527, 2010

4. Basch E, Prestrud AA, Hesketh PJ, et al: Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 29:4189-4198, 2011 [Erratum: J Clin Oncol 32:2117, 2014]
5. 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. Ann Oncol 21:v232-v243, 2010 (suppl 5)
6. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Antiemesis (version 2). Fort Washington, PA, National Comprehensive Cancer Network, 2014
7. Aapro M, Molassiotis A, Dicato M, et al: The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): The Pan European Emesis Registry (PEER). Ann Oncol 23:1986-1992, 2012
8. Bourdeanu L, Frankel P, Yu W, et al: Chemotherapy-induced nausea and vomiting in Asian women with breast cancer receiving anthracycline-based adjuvant chemotherapy. J Support Oncol 10:149-154, 2012
9. Tsuji D, Yokoi M, Suzuki K, et al: Influence of ABCB1 and ABCG2 polymorphisms on the antiemetic efficacy in patients with cancer receiving cisplatin-based chemotherapy: A TRIPLE pharmacogenomics study. Pharmacogenomics J 10.1038/tpj.2016.38 [epub ahead of print on May 31, 2016]
10. Perwitasari DA, Wessels JAM, van der Straaten RJHM, et al: Association of ABCB1, 5-HT3B receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy. Jpn J Clin Oncol 41:1168-1176, 2011
11. He H, Yin J-Y, Xu Y-J, et al: Association of ABCB1 polymorphisms with the efficacy of ondansetron in chemotherapy-induced nausea and vomiting. Clin Ther 36:1242-1252.e2, 2014
12. Chan A, Shwe M, Gan Y, et al: Trajectory and risk factors for chemotherapy-induced nausea and vomiting in Asian patients with head and neck cancer. Head Neck 37:1349-1357, 2015
13. Chan HK, Ismail S: Side effects of chemotherapy among cancer patients in a Malaysian general hospital: Experiences, perceptions and informational needs from clinical pharmacists. Asian Pac J Cancer Prev 15:5305-5309, 2014
14. Shih V, Wan HS, Chan A: Clinical predictors of chemotherapy-induced nausea and vomiting in breast cancer patients receiving adjuvant doxorubicin and cyclophosphamide. Ann Pharmacother 43:444-452, 2009
15. Williams PD, Lopez V, Ying CS, et al: Symptom monitoring and self-care practices among oncology adults in China. Cancer Nurs 33:184-193, 2010
16. Yap KY, Low XH, Chan A: Exploring chemotherapy-induced toxicities through multivariate projection of risk factors: Prediction of nausea and vomiting. Toxicol Res 28:81-91, 2012
17. Chan A, Tan SH, Low XH, et al: Antiemetic effectiveness and nausea and vomiting incidence during capecitabine and oxaliplatin chemotherapy. Nurs Res 61:405-412, 2012
18. Kim HK, Hsieh R, Chan A, et al: Impact of CINV in earlier cycles on CINV and chemotherapy regimen modification in subsequent cycles in Asia Pacific clinical practice. Support Care Cancer 23:293-300, 2015
19. Chan A, Low XH, Yap KY: Assessment of the relationship between adherence with antiemetic drug therapy and control of nausea and vomiting in breast cancer patients receiving anthracycline-based chemotherapy. J Manag Care Pharm 18:385-394, 2012
20. Poon KS, Un MK, Low XH, et al: Impact of cancer-related fatigue on chemotherapy-induced nausea and vomiting in Asian cancer patients. Pharmacoepidemiol Drug Saf 22:1345-1351, 2013
21. Hsieh RK, Chan A, Kim HK, et al: Baseline patient characteristics, incidence of CINV, and physician perception of CINV incidence following moderately and highly emetogenic chemotherapy in Asia Pacific countries. Support Care Cancer 23:263-272, 2015
22. Olver I: Assessing the burden and management of chemotherapy induced emesis in the Asia/Pacific region. Support Care Cancer 23:251-252, 2015
23. Osoba D, Zee B, Pater J, et al: Determinants of postchemotherapy nausea and vomiting in patients with cancer. J Clin Oncol 15:116-123, 1997
24. Hilarius DL, Kloeg PH, van der Wall E, et al: Chemotherapy-induced nausea and vomiting in daily clinical practice: A community hospital-based study. Support Care Cancer 20:107-117, 2012
25. Keefe DM, Chan A, Kim HK, et al: Rationale and design of the Pan Australasian Chemotherapy-Induced Emesis Burden of Illness study. Support Care Cancer 23:253-261, 2015
26. Yu S, Burke TA, Chan A, et al: Antiemetic therapy in Asia Pacific countries for patients receiving moderately and highly emetogenic chemotherapy—A descriptive analysis of practice patterns, antiemetic quality of care, and use of antiemetic guidelines. Support Care Cancer 23:273-282, 2015
27. Horne R, Graupner L, Frost S, et al: Medicine in a multi-cultural society: The effect of cultural background on beliefs about medications. Soc Sci Med 59:1307-1313, 2004

28. Multinational Association of Supportive Care in Cancer: MASCC/ESMO antiemetic guideline 2016. http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_2016_v.1.2.pdf
29. Hesketh PJ, Grunberg SM, Gralla RJ, et al: The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—The Aprepitant Protocol 052 Study Group. J Clin Oncol 21:4112-4119, 2003
30. Hu Z, Cheng Y, Zhang H, et al: Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: A randomized, double-blind, placebo-controlled phase III trial. Support Care Cancer 22:979-987, 2014
31. Botrel TE, Clark OA, Clark L, et al: Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT3R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: Systematic review and meta-analysis. Support Care Cancer 19:823-832, 2011
32. Grunberg SM, Koeller JM: Palonosetron: A unique 5-HT3-receptor antagonist for the prevention of chemotherapy-induced emesis. Expert Opin Pharmacother 4:2297-2303, 2003
33. Merck Sharp & Dohme: EMEND (aprepitant) capsules, for oral use. Highlights of prescribing information, 2015. https://www.merck.com/product/usa/pi_circulars/e/emend/emend_pi.pdf
34. Chan SL, Jen J, Burke T, et al: Economic analysis of aprepitant-containing regimen to prevent chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy in Hong Kong. Asia Pac J Clin Oncol 10:80-91, 2014
35. Lopes G, Burke T, Pellissier J, et al: Aprepitant for patients receiving highly emetogenic chemotherapy: An economic analysis for Singapore. Value Health Regional Issues 1:66-74, 2012
36. Hassan BA, Yusoff ZB: Genetic polymorphisms in the three Malaysian races effect granisetron clinical antiemetic actions in breast cancer patients receiving chemotherapy. Asian Pac J Cancer Prev 12:185-191, 2011
37. Philippines MIMS: Nasea: Concise prescribing information. http://www.mims.com/philippines/drug/info/nasea
38. Huang JQ, Zheng GF, Deuson R, et al: Do 5-hydroxytryptamine3 receptor antagonists (5-HT3) improve the antiemetic effect of dexamethasone for preventing delayed chemotherapy-induced nausea and vomiting (CINV)? A meta-analysis of randomized controlled trials. J Clin Oncol 22, 2004 (suppl; abstr 6037)
39. Roila F, Ruggeri B, Ballatori E, et al: Aprepitant versus metoclopramide, both combined with dexamethasone, for the prevention of cisplatin-induced delayed emesis: A randomized, double-blind study. Ann Oncol 26:1248-1253, 2015
40. Health Sciences Authority of Singapore: Drug safety information No. 57: Restrictions on the use of metoclopramide-containing products, 2015. http://www.pss.org.sg/sites/default/files/e-bulletin/issue_108/no_57_restrictions_on_the_use_of_metoclopramide-containing_products_23jul2015.pdf
41. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al: Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: Results of a phase III, single-dose trial versus dolasetron. Cancer 98:2473-2482, 2003
42. Gralla R, Lichinitser M, Van Der Vegt S, et al: Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: Results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 14:1570-1577, 2003
43. Celio L, Bonizzoni E, Bajetta E, et al: Palonosetron plus single-dose dexamethasone for the prevention of nausea and vomiting in women receiving anthracycline/cyclophosphamide-containing chemotherapy: Meta-analysis of individual patient data examining the effect of age on outcome in two phase III trials. Support Care Cancer 21:565-573, 2013
44. Albany C, Brames MJ, Fausel C, et al: Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: A Hoosier Oncology Group study. J Clin Oncol 30:3998-4003, 2012
45. Murakami M, Hashimoto H, Yamaguchi K, et al: Effectiveness of palonosetron for preventing delayed chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy in patients with gastrointestinal cancer. Support Care Cancer 22:905-909, 2014
46. Keat CH, Ghani NA: Cost-effectiveness analysis of granisetron-based versus standard antiemetic regimens in low-emetogenic chemotherapy: A hospital-based perspective from Malaysia. Asian Pac J Cancer Prev 14:7701-7706, 2013
47. Chan A, Kim HK, Hsieh RK, et al: Incidence and predictors of anticipatory nausea and vomiting in Asia Pacific clinical practice—A longitudinal analysis. Support Care Cancer 23:283-291, 2015
48. de Wit R, de Boer AC, vd Linden GH, et al: Effective cross-over to granisetron after failure to ondansetron, a randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. Br J Cancer 85:1099-1101, 2001

49. Segawa Y, Aogi K, Inoue K, et al: A phase II dose-ranging study of palonosetron in Japanese patients receiving moderately emetogenic chemotherapy, including anthracycline and cyclophosphamide-based chemotherapy. Ann Oncol 20:1874-1880, 2009

50. Sigsgaard T, Herrstedt J, Christensen P, et al: Antiemetic efficacy of combination therapy with granisetron plus prednisolone plus the dopamine D2 antagonist metopimazine during multiple cycles of moderately emetogenic chemotherapy in patients refractory to previous antiemetic therapy. Support Care Cancer 8:233-237, 2000

51. Navari RM, Nagy CK, Gray SE: The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 21:1655-1663, 2013

52. Yap KY, Low HX, Koh KS, et al: Feasibility and acceptance of a pharmacist-run tele-oncology service for chemotherapy-induced nausea and vomiting in ambulatory cancer patients. Telemed J E Health 19:387-395, 2013

53. Chan A, Shih V, Chew L: Evolving roles of oncology pharmacists in Singapore: A survey on prescribing patterns of antiemetics for chemotherapy induced nausea and vomiting (CINV) at a cancer centre. J Oncol Pharm Pract 14: 23-29, 2008