review article

Cheaper Options in the Prevention of Chemotherapy-Induced Nausea and Vomiting

abstract

Chemotherapy-induced nausea and vomiting (CINV) is a common challenge in oncology practice for which there are expensive guideline-based treatment options. Although supportive care in cancer adds significantly to the overall cost, the discussion of unaffordability of anticancer treatment frequently only revolves around the targeted drugs and immunotherapies. In this review, we highlight the available cost-saving strategies and recent updates in preventing CINV in patients with cancer. This is the first work, to our knowledge, to review specifically the less expensive alternatives in CINV prevention, which is particularly important for those working in resource-limited settings. Whereas patients in these settings often cannot afford expensive antiemetics, we now have the science to offer cheaper, more affordable options without necessarily compromising efficacy.

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a common challenge in modern oncology practice. For many patients with cancer, CINV is one of their worst fears.[1,2] Studies have shown that CINV can adversely affect quality of life, lead to change in treatment plans, and increase the use of health care resources.[3-5] It has also been demonstrated that clinicians frequently underestimate the incidence of CINV.[6]

The economic feasibility of anticancer treatment has been a matter of huge debate and discussion. The National Comprehensive Cancer Network (NCCN) has recently announced that it will publish cancer treatment guidelines that cater to the needs of resource-limited countries. Such guidelines for cervical cancer are already in place,[7] and a position paper by the European Society for Medical Oncology regarding decreasing the cost of anticancer treatment has also been published.[8] Despite the enthusiasm for reducing the high cost of cancer treatment, the high cost of supportive care for patients with cancer is frequently ignored. Antiemetics used in the prevention of CINV are often expensive, and because they are used with every treatment cycle, the cost of these agents adds significantly to the overall cost of treatment.

The current guidelines-based practice for highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) include the use of antiemetic drugs aprepitant and palonosetron[9,10]; both of these agents are expensive (Table 1). In resource-limited settings, the cost of these agents can be greater than the cost of the chemotherapy with which they are prescribed, and justifying the cost to patients is difficult.[11] These agents are also not easily available in developing and underdeveloped countries; however, evidence exists that supports the use of other less costly alternatives that are also effective in preventing CINV. In this article, we will review updates in the prevention of CINV that explore economically cheaper options. Oncologists in both developing and developed countries should be familiar with these approaches because it is common for patients not to be able to afford these expensive treatments, which can make guideline-based practice impossible. Furthermore, reducing the overall cost of cancer treatment is a collective responsibility we all share.

METHODS

A literature search was conducted in PubMed by using the search terms chemotherapy-induced nausea and vomiting, CINV, chemotherapy, nausea, vomiting, and emesis in various combinations. The search was conducted in June 2015 without any date restrictions. We included only those studies published in English and that were relevant to cost reduction in CINV treatment. We

Table 1 – Cost of Commonly Used Antiemetic Drugs in CINV in the United States

Antiemetic Drug	Cost in US Dollars
Aprepitant set (125, 80, 80 mg)	647.50
Palonosetron 0.25 mg IV	493.20
Ondansetron 8 mg	40
Olanzapine 10 mg	23.30
Metoclopromide 10 mg	2.48
Dexamethasone 8 mg	1.98
Prochlorperazine 10 mg	2.73

NOTE. Cost in US dollars has been referenced from Lexicomp in June 2015 and may vary. Wherever possible, oral medications have been chosen for cost calculation. All costs except aprepitant are per tablet and dose.
Abbreviation: CINV, chemotherapy-induced nausea and vomiting.

also conducted a manual search of the reference lists of the selected studies to incorporate a comprehensive list of studies for this review.

Olanzapine

Olanzapine is a relatively inexpensive and widely available agent that has been in use for a long time as an atypical antipsychotic. It targets not only the dopaminergic receptors (D1 to D5) that are responsible for antipsychotic properties but also the serotonergic, adrenergic, histaminergic, and muscarinic receptors.[12-15] These receptors are known to play a role in the emesis reflex, and the ability to target multiple receptors with a single oral medication is an advantage of this drug. Olanzapine has now been included as an alternative to an aprepitant-containing regimen in the NCCN guidelines for the prevention of CINV resulting from HEC and MEC.[9] Use of olanzapine represents a cost reduction of approximately US$100 to US$500 in one cycle (Table 2), which is significant for both patients and health care systems. Evidence for the use of olanzapine to prevent emesis associated with HEC comes from a randomized study by Navari et al[17] that compared treatment with aprepitant, palonosetron, and dexamethasone (APD) with treatment with olanzapine, palonosetron, and dexamethasone (OPD) in 257 patients. The primary end point was overall complete response (CR). The study found a numerical advantage for the OPD regimen with regard to overall CR, acute CR, and delayed CR, and OPD demonstrated both a numerical and a statistical advantage for overall nausea control and delayed nausea control (Table 3).[17] No treatment-related adverse effects were observed in either arm, and there were no significant differences in the two arms with regard to any of the MD Anderson Cancer Center symptom scores. This study has been criticized for being open label and for not indicating whether it was a superiority or an inferiority trial[18,19]; however, there is still credible evidence to support the use of olanzapine because vomiting is a parameter that is not affected by blinding, and all patients were chemotherapy naïve and had not previously received either of the antiemetic regimens. Moreover, the control of delayed and overall nausea was improved by $> 30\%$. It should be noted that the OPD regimen contained only a single dose of dexamethasone 20 mg on day 1 and a dosage of olanzapine 10 mg/d was continued for $\leqslant 4$ days.

Another phase III trial randomly assigned 229 Chinese patients being treated with HEC or MEC to treatment groups of either olanzapine, azasetron, and dexamethasone or azasetron and dexamethasone.[20] The trial found that the addition of olanzapine significantly improved the CR rates of delayed nausea and vomiting as well as quality of life (QoL), with no significant difference for acute nausea and vomiting.[20] An important caveat of this study, however, is the use of azasetron as a 5-HT_3 (5-hydroxytryptamine-3) inhibitor, which was later shown to be inferior to ondansetron for the prevention of delayed CINV.[21] Nevertheless, this study demonstrated impressive improvements in delayed nausea CR (HEC, 39.2%; MEC, 25.0%), delayed vomiting CR (HEC, 22.0%; MEC, 13.4%), overall nausea CR (HEC, 41.3%; MEC, 26.6%), and overall vomiting CR (HEC, 22.0%; MEC, 13.4%). This study also showed improvements in QoL. Some beneficial antidepressant effect of this atypical antipsychotic also cannot be ruled out in this setting.[20]

Table 2 – Cost Analysis of OPD Versus APD Regimen by Country

Country	Cost of APD Regimen, Dollars	Cost of OPD Regimen, Dollars	Cost Saving, Dollars
United States	1,143.00	589.00	554.00
Australia	169.00	72.00	97.00

NOTE. Cost in Australia has been referenced from Hocking and Kichenadasse.[16]
Abbreviations: APD, aprepitant (days 1 to 3), palonosetron (day 1), dexamethasone (days 1 to 4); OPD, olanzapine (days 1 to 4), palonosetron (day 1), dexamethasone (day 1).

Table 3 – Efficacy of OPD Versus APD Regimen

Parameter	APD Regimen	OPD Regimen	*P*
CR acute	87	97	NS
CR delayed	73	77	NS
CR overall	73	77	NS
Nausea control acute	87	87	NS
Nausea control delayed	38	69	< .01
Nausea control overall	38	69	< .01

NOTE. Taken from the Navari et al.[17]

Abbreviations: APD, aprepitant (days 1 to 3), palonosetron (day 1), dexamethasone (days 1 to 4); CR, complete response (no emesis, no rescue); OPD, olanzapine (days 1 to 4), palonosetron (day 1), dexamethasone (day 1); NS, not significant.

A randomized study that compared olanzapine with aprepitant was presented at the 2009 ASCO Annual Meeting.[22] This was a double-blind, placebo-controlled study in 18 chemotherapy-naïve patients who were receiving HEC, and results showed that olanzapine obtained a numeric advantage in all parameters—acute CR, delayed CR, and rates of nausea in anticipatory, acute, and delayed periods—compared with aprepitant.

A meta-analysis of six studies involving 726 patients, of whom 441 were Chinese, who received HEC and MEC found that olanzapine-containing antiemetic regimens were more effective than non–olanzapine-containing regimens, especially for delayed CINV.[23] However, only two of these studies used the standard guideline regimen (5-HT_3 + dexamethasone + neurokinin 1 [NK-1] antagonist) as the control arm. Another meta-analysis of 488 patients from three trials further confirmed the efficacy and safety of olanzapine-containing regimens for CINV prevention as well as for olanzapine as a single agent for treatment of breakthrough CINV.[16]

Many studies have demonstrated that it is more difficult to control nausea than it is vomiting; however, olanzapine studies have shown that the agent is particularly helpful in controlling nausea. It should be noted, however, that OPD has been approved only in the NCCN guidelines,[9] whereas guidelines by ASCO and the European Society for Medical Oncology/Multinational Association of Supportive Care in Cancer have yet to include olanzapine for CINV prevention.[10,24]

Although debate exists over the prophylactic use of olanzapine for the prevention of HEC and MEC CINV, use of olanzapine in breakthrough CINV is relatively well accepted. In a double-blind, phase III randomized trial among 276 patients receiving HEC, olanzapine was found to be significantly better than metoclopramide in the control of breakthrough emesis and nausea. During the 72-hour observation period, the percentages of patients with no vomiting and no nausea were 70 and 68 versus 31 and 23 in olanzapine versus metoclopramide groups, respectively ($P < .01$ for both vomiting and nausea).[25]

Common adverse effects associated with olanzapine, as experienced from its use in psychiatric patients, include sedation, sleepiness, weight gain, hyperglycemia, dyslipidemia, orthostatic hypotension, extrapyramidal symptoms such as akathisia, and anticholinergic effects of dry mouth, constipation, asthenias, tremors, dyspepsia, and dizziness.[26-28] Decreased seizure threshold, diabetes, prolongation of QTc interval, and, although rare, neuroleptic malignant syndrome have also been reported with use of olanzapine in psychiatric practice.[18] Weight gain and increased appetite could actually be positive effects, given that many patients with cancer are cachectic. Care should be taken with patients on antihypertensive agents because olanzapine can potentiate hypotension. Olanzapine has been included in the Beers list of drugs to avoid in older adults with syncope and seizures.[29] Of note, these adverse effects were conspicuously absent in the clinical studies of olanzapine in CINV, which suggests that the short-term use of the drug in such instances as in the prevention or treatment of CINV is safe.

The risk of drug interaction must be considered when administering any antiemetic. Olanzapine is metabolized by CYP1A2 and CYP2D6, and, as a result, inhibitors of CYP1A2, such as fluvoxamine, decrease olanzapine clearance, whereas inducers of CYP1A2, such as omeprazole, rifampin, and carbamazepine, increase olanzapine clearance. Inhibitors of CYP2D6 have a relatively weaker impact on olanzapine clearance. It is important to note that drug interactions with olanzapine are few compared with aprepitant.[18]

In conclusion, an olanzapine-containing regimen is a cost-reducing alternative to an aprepitant-containing regimen. The role of other 5-HT_3 antagonists in combination with olanzapine and dexamethasone should also be explored because the cost of palonosetron is more than ten times that of first-generation 5-HT_3 antagonists. Although a randomized, double-blinded study is desirable, all available studies suggest favorable outcomes with olanzapine. Moreover, there are many hurdles to conducting large, phase III trials in the supportive care field. As currently available data support the use of olanzapine, and as there is no clear data to

suggest that administering an NK-1 inhibitor is superior, an olanzapine-containing treatment regimen should be an obvious choice, especially for patients who cannot afford costlier drugs. The cost savings associated with the use of OPD versus APD in various countries is highlighted in Table 2.

Ginger

Ginger is known to exert antiemetic properties. Although the exact mechanism of action is unknown, possible mechanisms hypothesized include regulation of GI secretions and motility[30,31] as well as interaction with 5-HT_3 receptors.[32] Ginger has been known to be effective in cisplatin-induced emesis in animal models.[33,34]

In a large, double-blind, randomized study, 744 patients with cancer were randomly assigned to three different doses of ginger (0.5 g, 1.0 g, or 1.5 g) or a placebo. All patients received a 5-HT3 antagonist on day 1 of all cycles and three capsules of ginger 250 mg or placebo twice a day for six days, beginning three days before day 1. Of 576 patients included in the final analysis, of which 91% were female, all doses of ginger significantly reduced the severity of acute nausea on day 1 compared with placebo (P = .003). The largest reduction in nausea intensity was observed with doses 0.5 g and 1.0 g (P = .017 and .036, respectively).[35] In the delayed phase, no significant benefit was noted. Similar results in acute phase, but not delayed phase, CINV were obtained in an open-label study of ginger plus granisetron plus dexamethasone in patients with breast cancer.[36] These studies suggest a use for ginger in the treatment of CINV, at least for acute nausea. However, other studies have found a role for ginger in the treatment of delayed nausea as well.[37,38]

Another advantage of ginger lies in the fact that it does not have significant adverse effects. In fact, it is commonly used as a spice or flavoring agent in the food of many South Asian countries. The reported adverse effects of ginger include abdominal discomfort, heartburn, diarrhea, and inhibition of platelet aggregation leading to bleeding; however, these are of a more theoretical interest.[35,39]

A systematic review of the efficacy of ginger in CINV that was performed in 2013 reviewed seven randomized controlled studies, of which all but two favored the use of ginger in the prevention of CINV.[39] The two studies that failed to show a benefit were severely flawed. The first study enrolled only 36 participants, of which 13 were excluded as a result of nonadherence.[40] The second study had a larger sample size (N = 129) but compared ginger versus a placebo in combination with 5-HT_3 with or without aprepitant.[41] Of the participants, > 31% and >43% had received aprepitant and palonosetron, respectively. Because effective antiemetics had already been administered to many participants, ginger could not have provided any additive effect. These ginger studies have several problems, one of which is the standardization of dose in ginger capsules, and a second being that the aroma or smell of ginger makes true blinding difficult. However, blinding strategies have been developed and used effectively.[35]

In conclusion, ginger seems to be a cheap and attractive adjunct for CINV prevention. Pillai et al[38] found that, compared with placebo, ginger plus ondansetron plus dexamethasone was effective in the prevention of both acute and delayed CINV in children and young adults receiving HEC. This is a promising finding, and such strategies should be investigated and validated in larger patient populations. If validated, this regimen could be of immense value in terms of cost savings. On the basis of a study by Ryan et al,[35] thus far the largest, well-conducted study of the effect of ginger in CINV, ginger could at least be encouraged in the setting of the trial inclusion criteria, that is, for patients with a history of CINV in a previous cycle and for those with controlled emesis but continued nausea.

Dexamethasone Sparing

For HEC and MEC, guidelines recommend the use of dexamethasone for the first 4 days and the first 3 days of the treatment cycle, respectively, for the prevention of delayed nausea and vomiting. In 2010, Aapro et al[42] investigated whether dexamethasone could be omitted altogether on days 2 and 3 in 300 chemotherapy-naïve patients receiving an antiemetic regimen of palonosetron plus dexamethasone with AC (anthracycline, cyclophosphamide) -based chemotherapy. Their results showed that dexamethasone on only the first day of treatment with AC was not inferior to dexamethasone continued for the first 3 days with respect to acute CR (69.5 *v* 68.5%, respectively), delayed CR (62.3 *v* 65.8%, respectively), and overall CR (53.6 *v* 53.7%, respectively). An Italian phase III, open-label study, randomly assigned 332 patients receiving MEC to palonosetron and dexamethasone on day 1 only versus palonosetron on day 1 only and dexamethasone on days 1 to 3. This study showed that a dexamethasone-sparing strategy was not inferior in terms of overall, acute,

and delayed CR rates, especially for non–AC-containing MEC.[43] A prespecified retrospective analysis of the two studies found that a dexamethasone-sparing regimen is not associated with a significant loss in overall antiemetic protection in women undergoing AC-containing chemotherapy, regardless of age.[44]

A recent phase III, randomized, open-label Japanese study of 305 patients also demonstrated that dexamethasone may be omitted on days 2 and 3 for non–AC-containing MEC, with administration of palonosetron and dexamethasone on day 1 only showing no inferiority in overall CR compared with palonosetron and dexamethasone on days 1 to 3 (66.2% *v* 63.6%, respectively).[45] This study administered palonosetron 0.75 mg, which is the commonly used dose in Japan. Netupitant-palonosetron is a netupitant (an NK-1 antagonist) plus palonosetron combination that has recently been included in the NCCN guidelines.[9] Netupitant-palonosetron and dexamethasone are also administered on day 1 only, whereas dexamethasone is not necessary to be administered on subsequent days.[46]

A nonrandomized, phase II Italian trial demonstrated that dexamethasone can be safely omitted from AC-containing MEC in patients with breast cancer (with palonosetron administered on day 1 only) because other corticosteroids, such as prednisone and hydrocortisone, are used by default for chemotherapy premedication.[47]

Although dexamethasone is not expensive, a dexamethasone-sparing strategy is cheaper when considering the overall cost of managing the wide variety of adverse effects that are associated with corticosteroid use, such as insomnia, GI upset, agitation, increased appetite, weight gain, and skin rash.[48] This implies that a dexamethasone-sparing strategy can both save money and improve QoL.

Aprepitant Sparing for Delayed Emesis

A recent study by the Italian Group for Antiemetic Research explored an aprepitant-sparing strategy for the prevention of delayed CINV in AC-containing MEC (dexamethasone *v* aprepitant on days 2 and 3) after APD on day 1. This study showed that dexamethasone and aprepitant had similar efficacy and toxicity in preventing delayed emesis,[49] which represents cost savings of approximately US$350 for dexamethasone over aprepitant. Although these studies have been criticized for the potential confounding by palonosteron,[50] it should be noted that APD followed by aprepitant is a guideline-based practice. That APD followed by dexamethasone alone is effective is important, given the cost savings of this strategy.

One multiarm, double-blind, randomized trial showed that palonosetron and granisetron had similar efficacy in preventing delayed nausea (prochlorperazine and not dexamethasone was administered on days 2 and 3), and that effects from the addition of prochlorperazine was similar to those of the addition of aprepitant.[51] The primary end point of this study was average nausea assessed four times per day on days 2 and 3, which is a matter for criticism.[52] However, an important finding from this study is that dexamethasone and prochlorperazine could substitute for aprepitant to prevent delayed nausea (86% of patients experienced no benefit from aprepitant over prochlorperazine), and that palonosetron is similarly effective compared with granisetron. Most of the studies on aprepitant in delayed nausea have compared aprepitant with placebo or dexamethasone or 5-HT_3 alone and found positive results.[53-56] However, this study, where aprepitant was compared with dexamethasone and prochlorperazine,[51] and another study by Schmoll et al,[57] in which aprepitant was compared with dexamethasone and 5-HT3, showed no difference between groups for delayed nausea. Thus, dexamethasone and prochlorperazine could potentially provide a cheaper efficacious alternative to the expensive aprepitant.

Metoclopramide

Metoclopramide is a dopamine receptor antagonist that was used as a first-line therapy for the prevention of CINV before 5-HT_3 antagonists were introduced.[58] Current guidelines, however, suggest metoclopramide only for the treatment of breakthrough emesis. A randomized, double-blind trial by the Italian Group for Antiemetic Research investigated the role of metoclopramide versus aprepitant in the prevention of cisplatin-induced, delayed CINV.[59] All patients received APD on day 1 and were then randomly assigned to aprepitant 80 mg orally once per day on days 2 and 3 and dexamethasone 8 mg on days 2 to 4 versus metoclopramide 20 mg four times daily on days 2 to 4 and dexamethasone 8 mg twice a day on days 2 to 4. Although limited by poor accrual, this study showed a numeric advantage for metoclopramide plus dexamethasone over aprepitant and dexamethasone for CR rate (82.5% *v* 80.3%, respectively). However, it failed to show the superiority of aprepitant and dexamethasone over metoclopramide and dexamethasone in the prevention of delayed emesis in HEC. Secondary

end points—complete protection, total control, no vomiting, no nausea, and score of functional living—were similar between both cohorts[59]. Given that the efficacy of both regimens were similar and that the cost of aprepitant is seven times that of metoclopramide, the choice of regimen is obvious, especially in economically constrained situations.

The adverse effects of metoclopramide include neurologic effects, such as extrapyramidal symptoms and tardive dyskinesia. Therefore, the European Medicines Agency, but not the US Food and Drug Administration, has restricted the use of metoclopramide to a maximum of 5 days, 30 mg/d.[60] Metoclopramide is also a drug to avoid in older adults according to the Beers Criteria[29]; however, no extrapyramidal adverse effects were observed in the Italian study of metolcopramide in CINV prevention.[59] Although the loss of power resulting from poor accrual of this study has been pointed out as a pitfall by some critics,[19] the authors' defense of having taken a lower margin of difference for sample calculation, numeric advantage of metoclopramide arm in all but one of the primary and secondary end points as well as corroboration by similar findings in the past attest to the reliability of this study. Therefore, this study should not be regarded as having poor accrual and, therefore, no validity, but should be taken by clinicians as a viable alternative, especially in resource-limited settings or settings for which alternatives are needed. Further research on cost effectiveness by testing this with a first-generation 5-HT_3 regimen on day 1 or with OPD is needed.

In conclusion, there has been substantial research and progress in exploring cheaper alternatives for the prevention of CINV. With scientific data supporting the use of alternative antiemetic regimens, we should not hesitate to practice cheaper CINV prevention strategies, especially in resource-limited settings. Because trials in alternative drugs have shown better or comparable results to expensive counterparts, these regimens should also be explored in developed countries. A dexamethasone-sparing strategy could be used when aprepitant and palonosetron regimens are used, as shown by the trials. The efficacy of ginger in preventing CINV may be considered by oncologists in resource-limited settings who care for poor patients.

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