

Treatment of Chemotherapy-induced Nausea in Cancer Patients

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Abstract

For over 30 years, chemotherapy-induced nausea and vomiting have been the most severe and troublesome symptoms for cancer patients receiving chemotherapy. Unresolved chemotherapy-induced nausea and vomiting can lead to metabolic disorders, dehydration, nutritional depletion and oesophageal tears, and can reduce the daily functioning and quality of life of and interfere with treatment schedules. Despite the widespread use of antiemetics, chemotherapy-induced nausea continues to be problematic. Unlike vomiting, nausea is a subjective and unobservable phenomenon, making it extremely difficult to accurately assess and treat. Current research suggests that management of chemotherapy-induced nausea should focus on treating the symptoms before they occur rather than after they develop. This article highlights evidence-based interventions for the treatment of chemotherapy-related nausea.

Keywords

Chemotherapy, nausea, vomiting

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Cancer patients rate nausea the most distressing side effect of chemotherapy.^{1,2} Chemotherapy-induced nausea continues to be reported by up to 70% of adult patients receiving moderately and highly emetogenic chemotherapy agents and 58% of school-age and adolescent-age children receiving highly emetogenic chemotherapy, despite the extensive use of antiemetics.^{3,4} Currently, the standard of care for chemotherapy-induced nausea is antiemetics, most notably serotonin (5-HT₃) receptor antagonist. However, research has shown that antiemetics are clinically effective against emesis but not nausea.^{5–7} Successful treatments have proved to be those given prophylactically before chemotherapy to prevent the onset of nausea and/or vomiting.^{8–10} Interventions for nausea administered after the insult of chemotherapy are ineffective. Furthermore, clinical studies have shown that control of chemotherapy-induced nausea and vomiting in the acute period correlates with the control of delayed nausea and vomiting.

Nausea is a subjective and unobservable phenomenon that originates from a connection between the brain and the gut.^{8,11} The gut contains more neuronal innervations than the spinal cord. Nausea is not the same as vomiting and is most accurately measured by self-assessment tools, such as diaries and visual analogue scales (VAS).¹² Most antiemetic medications are antagonist for neurotransmitter receptors located in the gut and designed to inhibit the emetic signalling of these receptors. Although antiemetics do not completely control feelings of nausea, the biological mechanism for nausea most likely involves these neurotransmitters in the gut, such as serotonin, neurokinin and dopamine. Previously reported risk factors for severe

nausea include female gender, young age, prescribed chemotherapy regimen and vomiting during previous chemotherapy, as well as the expectancy of nausea of patients.^{11–15} Roscoe et al. showed that women who believed they would have severe nausea after chemotherapy were five times more likely to experience severe nausea compared with those who did not believe they would have severe nausea.¹⁵

Chemotherapy-induced nausea can be categorised into three types: anticipatory, acute and delayed. Anticipatory nausea occurs before the start of chemotherapy in anticipation of the treatment and develops in 8–20% of patients.^{7,16,17} Anticipatory nausea is reported by approximately 20% of patients at any one chemotherapy cycle and by 25–30% of patients by the fourth chemotherapy cycle. The incidence of anticipatory nausea reported in two studies of children varied from 15 to 54%, partially explained by the degree of emetic control of the previous cycle.^{18,19} No pharmacological agents have had success in treating anticipatory nausea once it has occurred.^{17,20,21} By contrast, the behavioural method of systematic desensitisation can be effective, but it is not readily available in most clinic settings.^{20,22} Acute nausea occurs within 24 hours post-chemotherapy, whereas delayed nausea occurs over 24 hours and up to five days post-chemotherapy. The majority of patients report the most severe nausea on day one of chemotherapy and are less likely to have severe nausea on subsequent days if they do not experience it on day one.²³ Delayed nausea occurs in approximately 50–80% of patients and is most often associated with highly emetogenic chemotherapy regimens, such as doxorubicin and cisplatin. Delayed post-chemotherapy nausea and vomiting are difficult

problems as they typically do not develop until after the patient has left the treatment location, are often under-reported and are not well controlled by currently available antiemetics.^{11,24}

All in all, there is still room for improvement of control of nausea associated with chemotherapy for cancer. Furthermore, current antiemetics have been associated with significant adverse effects, such as sedation, extrapyramidal side effects and hypotension (associated with dopamine antagonists), as well as headache, diarrhoea or constipation (associated with serotonin [5-HT₃] receptor antagonists). A desirable attribute in any substitute or additional^{6,7,9,10} antiemetic medication would be the absence of clinically significant adverse effects. Thus far, two non-invasive and non-toxic interventions have demonstrated promising control of chemotherapy-induced nausea when used in combination with routine antiemetics.

Antiemetics

The most commonly used treatment for chemotherapy-induced nausea and vomiting from moderately and highly emetogenic regimens is a combination of serotonin (5-HT₃) receptor antagonists, a steroid (dexamethasone), and a neurokinin-1 (NK1) receptor antagonist (aprepitant).^{11,13} The most commonly used antiemetics are the serotonin (5-HT₃) receptor antagonists, including ondansetron (Zofran®), granisetron (Kytril®) and dolasetron mesylate (Anzemet®) and palonosetron. An ondansetron, dexamethasone and aprepitant regimen was able to protect 66–78% of patients from emesis and 50% from nausea during the first cycle of cisplatin-based chemotherapy.¹¹ Serotonin (5-HT₃) antiemetics do not significantly reduce delayed nausea and emesis. By contrast, dexamethasone and aprepitant are recommended against delayed nausea and emesis.^{11,13} Studies have shown that dexamethasone is the most potent antiemetic for prevention of delayed nausea and vomiting. Furthermore, aprepitant increases the efficacy of serotonin (5-HT₃) antiemetics plus dexamethasone regimens to reduce both acute and delayed chemotherapy-induced nausea and vomiting during highly emetogenic regimens, such as cisplatin.^{8,11,25}

Other neurotransmitter receptors in the gut that are targets of antiemetic medications include dopamine, cannabinoid, histamine and cholinergic receptors. Dopamine receptor antagonist antiemetics, such as metoclopramide and metopimazine, are primarily used as rescue antiemetics.^{8,11} Cannabinoid receptor agonists have shown antiemetic effectiveness, but their use is restricted due to association with severe adverse events. Despite effectiveness against motion sickness, antihistamines and anticholinergics have no effect on chemotherapy-related nausea and vomiting.^{8,11}

Ginger Supplementation

Ginger, an ancient tuber mentioned in both the Bible and the Koran, is most known for its role as a flavouring agent for food in Asian and Indian recipes.²⁶ Since the 16th century, the dried aromatic rhizome (underground stem) of ginger (*Zingiber officinale* Roscoe), has also been used by practitioners of both Indian (Ayurvedic) and traditional Chinese medicine to treat gastrointestinal upsets such as nausea and excessive flatulence. North American folklore also recognises the ability of ginger to relieve gastrointestinal upsets including nausea. Ginger is also believed to be the only plant that can prevent symptoms of motion sickness and it has been approved for that use by Germany's Commission E, the agency responsible for regulating the use of herbal products in that country.²⁶ Ginger is on the the US

Food and Drug Administration (FDA) 'generally regarded as safe' (GRAS) list for up to 4g daily. Recently, ginger has been studied scientifically for its effect on nausea and vomiting associated with motion sickness, surgery and pregnancy.^{21,27–34}

Despite the fact that many patients use ginger for prevention or treatment of nausea and vomiting caused by chemotherapy for cancer, only seven studies were found that assessed the efficacy of ginger for chemotherapy-induced nausea and vomiting.¹⁴ All studies were in adults with cancer and five of the seven studies enrolled fewer than 60 subjects. In one of the larger studies, Zick et al. found no difference between placebo and two doses of ginger (1 and 2g) in the prevalence or severity of delayed or acute chemotherapy-induced nausea and vomiting in 162 adults reporting chemotherapy-induced nausea and vomiting with a previous identical chemotherapy cycle (of any emetogenicity).³⁵ Lack of effect could be partly attributed to starting ginger following the start of chemotherapy and an underpowered sample for the secondary aim testing acute effects. Four other small studies found significant reductions in nausea with ginger. In 41 patients being treated for leukaemia with cytosine arabinoside, subjects who received ginger (0.5g) along with Compazine® (prochlorperazine) prior to chemotherapy had significantly less severe nausea on the day of chemotherapy and on the following day than those taking the placebo capsules.³⁶ Another study compared ginger (1.5g) with psoralen in patients receiving methoxsalen (8-MOP) for extra-corporeal chemotherapy and found that the total nausea score was reduced by approximately one-third in those receiving ginger.³⁷ Sontakke et al. compared the effects of ginger (4g/day) with metoclopramide and ondansetron in controlling chemotherapy-induced nausea and vomiting in response to low-dose cyclophosphamide.³⁸ Ginger was equally effective as metoclopramide in achieving complete control, but both were less effective than ondansetron. In the only study demonstrating effectiveness of ginger to reduce delayed chemotherapy-induced nausea, Levine et al. also found less gastric dysrhythmia in subjects taking a high protein drink with 2g of ginger per day.³⁹

At the American Society of Clinical Oncology (ASCO) Annual Meeting 2009, our research group presented the largest study to date investigating the efficacy of ginger in reducing chemotherapy-induced nausea.¹⁰ We demonstrated that three daily doses of ginger (0.5, 1.0 and 1.5g) reduced acute chemotherapy-induced nausea, compared with placebo, in 644 adults receiving chemotherapy for primarily breast, lung and alimentary cancer (90% female, mean age 53 years). In contrast to the other chemotherapy-induced nausea and vomiting studies, we began the administration of ginger three days prior to chemotherapy. We conclude that cancer patients can alleviate chemotherapy-induced nausea by using ginger supplementation (0.5–1.0g daily), which is equivalent to quarter to half a teaspoon of ground ginger, along with the standard 5-HT₃ receptor antagonist antiemetics and dexamethasone.¹⁰ It is important to note that the ginger used in this study consisted of capsules containing a purified liquid extract equivalent to 250mg of ginger. The purified liquid extract concentrated the biologically active components of the ginger root, such as gingerols, zingerones and shogaols.²⁷ It is unclear whether ginger in other forms, such as tea, crystallised or raw, would show the same efficacy.

Acupressure

Acupressure has been used for centuries in traditional Chinese medicine to control nausea and vomiting.^{9,15,40} Acupressure involves acupoint stimulation of the pericardium 6 (P6) located on the anterior

surface of the wrist between the tendons of the flexor carpi radialis and the Palmaris longus. In 2005, Ezzo et al. published a meta-analysis concluding that acupressure significantly reduced acute chemotherapy-induced nausea when combined with standard antiemetics.⁴⁰ Common modalities for P6 stimulation include wristwatch-like devices consisting of an elastic band with an embedded stud, such as Relief-bands® or Seabands®. Although the overall effect of acupressure strongly suggests effectiveness against acute and delayed chemotherapy-induced nausea, the data are not conclusive.

New Approaches and Conclusions

Research studies suggest that a major factor in preventing or reducing nausea is treating the symptom before it occurs. Successful interventions for chemotherapy-induced nausea, such as ginger, are those that are administered before exposure to chemotherapy. Starting interventions a few days before chemotherapy allows the patient to prepare for chemotherapy and potentially minimise anxiety. Furthermore, the preventative approach provides the patient with a sense of control over the symptom. It is possible that antiemetic drugs would be more effective against nausea if given a day or two before chemotherapy. For example, a commonly prescribed serotonin (5-HT₃) receptor antagonist antiemetic, granisetron (Kytril®), is now available in a transdermal patch (Sancuso®, ProStraken, Inc.).⁴¹ Patients apply the patch one to two days before chemotherapy and leave it on for a total of five to seven days. According to research performed by ProStraken, Inc., Sancuso is more effective against chemotherapy-related nausea than the current standard antiemetic treatments. Sancuso is not yet readily available in the clinic setting, but has been approved by the FDA.

Additionally, the most effective interventions for chemotherapy-induced nausea have been combination treatments. Recently, olanzapine, an antipsychotic that blocks several receptors such as dopamine, serotonin, muscarinic cholinergic, adrenergic and histamine receptors, has demonstrated effectiveness against acute and delayed nausea and vomiting when combined with palonosetron and dexamethasone on day 1.⁴²

Promising and extensive research studies have identified two non-invasive and cost-effective techniques, ginger supplementation and acupressure, to aid in the reduction of nausea and improve quality of life in cancer patients receiving chemotherapy.^{9,10,40} Although there have been many medical advances in the field of vomiting and chemotherapy-induced nausea, the pathophysiology of chemotherapy-induced nausea is complex and remains unclear. Additional clinical trials are warranted to further understand the mechanism and obtain complete control of chemotherapy-induced nausea. ■



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