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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 esophageal tears, and can reduce patients' daily functioning and quality of life and interfere with treatment schedules.[1, 2] 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 review highlights evidence-based interventions for the treatment of chemotherapy-related nausea.

Keywords

chemotherapy; nausea; vomiting

Introduction

Cancer patients rate nausea the most distressing side effect of chemotherapy. Despite the extensive use antiemetics, 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.[3, 4] Currently, the standard of care for chemotherapy-induced nausea is antiemtics, most notably sertononin (5-HT3) receptor anatagonists. 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 most accurately measured by self-assessment tools, such as diaries and visual analog scales.[12] Most antiemetic medications are antagonist for neurotransmitter receptors located in the gut and designed to inhibit the emetic signaling of these receptors. Although antiemetics do not completely control feelings of nausea, the biological mechanism for nausea most likely involves these neurotransmitters

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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 patient's expectancy of nausea.[11-15] Roscoe *et al* showed that women who believe they would have severe nausea after chemotherapy were five times more likely to experience severe nausea compared to those who didn't believe they would have severe nausea.[15]

Chemotherapy-induced nausea can be categorized into three different types of nausea: anticipatory, acute and delayed nausea. 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 pharmacologic agents have had success in treating anticipatory nausea once it has occurred.[17, 20, 21] In contrast, the behavioral method of systematic desensitization 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. Majority of patients report the most severe nausea on Day 1 of chemotherapy and are less likely to have severe nausea on subsequent days if they do not experience it on Day 1.[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 underreported, and are not well-controlled by currently available antiemetics.[11, 24]

All in all, there is still room for improvement control of nausea associated with chemotherapy for cancer. Furthermore, current antiemetics have been associated with significant adverse effects, such as sedation, extra-pyramidal side effects and hypotension (associated with dopamine antagonists), as well as headache, diarrhea or constipation (associated with 5-HT_3 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 noninvasive and non-toxic interventions have demonstrating 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 anitemetics are the serotonin (5-HT3) receptor antagonists, including ondansetron (Zofran®), granisetron (Kytril®), and dolasetron mesylate (Anzemet,®), and palosetron. Ondansetron, dexamethasone, and aprepitant regimen was able to protect 66-78% of patients from emesis and 50% from nausea during first cycle of cisplatin-based chemotherapy.[11] Serotonin (5-HT3) antiemetics do not significantly reduce delayed nausea and emesis. In 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, canniboid, histamine, and cholinergic receptors. Dopamine receptor antagonist antiemetics, such as metoclopramide and metopimazine, are primarily used as rescue antiemetics.[8, 11] Cannibinoid receptor agonists have shown antiemetic effectiveness, but restricted in use due to association with severe adverse events. Despite effectiveness against motion sickeness, antihistamines and anticholinergics have no effect on chemotherapy-related nausea and vomiting.[8, 11]

Ginger Supplementation

Ginger, an ancient spice mentioned in both the Bible and the Koran, is most known for its role as a flavoring 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 recognizes the ability of ginger to relieve gastrointestinal upsets including nausea. Ginger is also believed to be the only herb 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] In the United States, ginger on the Food and Drug Administration's (FDA) "generally regarded as safe" (GRAS) list for up to 4 grams 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 sixty subjects. In one of the larger studies, Zick *et al* found no difference between placebo and two doses of ginger (1g 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. I n 41 patients being treated for leukemia with cytosine arabinoside, subjects who received ginger (0.5 g) 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 (1.5 gm) to psoralen in patients receiving 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) to metoclopromide and ondansetron in controlling CINV in response to low dose cyclophosphamide.[38] Ginger was equally effective as metoclopromide in achieving complete control, but both were less effective than ondansetron. In the only study demonstrating effectiveness of ginger to reduce delayed CIN, Levine *et al* found also found less gastric dysrhythmia in subjects taking a high protein drink with 2g of ginger per day.[39] There were only 28 subjects who remained unblended to study arm.

Our research group recently completed and presented, at the American Society of Clinical Oncology (ASCO) Annual Meeting 2009, the largest study to date investigating the efficacy of ginger in reducing chemortherapy-induced nausea.[10] We demonstrated that three different daily doses of ginger (0.5 gram, 1.0 gram, 1.5 grams) reduced acute chemotherapy-induced nausea, compared to placebo, in 644 adults receiving chemotherapy for primarily breast, lung, and alimentary cancer (90% female, mean age = 53). 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 to 1.0 gram daily), which is equivalent to ¼ to ½ 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 250 milligrams 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 if ginger in other forms, such as tea crystallized or raw would show the same efficacy.

Acupressure

Acupressure has been used for centuries in traditional Chinese medicine to control for 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 corpi 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 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 is not conclusive.

New Approaches and Conclusions

Research studies suggest that a key factor in preventing or reducing nausea is treating the symptom before it occurs. Successful interventions for chemotherapy-induced nausea, such as ginger, are those which were administered before exposure to chemotherapy. Starting interventions a few days before chemotherapy allows the patient to prepare for chemotherapy and potentially minimizes anxiety. Furthermore, the preventative approach provides the patient 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 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 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 anti-psychotic that blocks several receptors such as dopamine, serotonin, muscarine cholinergic, adrenergic, and histamine receptor, 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 noninvasive 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 chemotherapy-induced nausea and vomiting, 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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References

1. Bliss JM, Robertson B, Selby P. The effect of nausea and vomiting on quality of life measures. British Journal of Cancer. 1992; 66(19 Suppl):814–823.
2. Schwartzberg LS. Chemotherapy-induced nausea and vomiting: Clinician and patient perspectives. Journal of Supportive Oncology. 2007; 5(2 Suppl):5–12. [PubMed: 17366928]
3. Hickok JT, Roscoe JA, Morrow GR, et al. Use of 5-HT3 receptor antagonists to prevent nausea and emesis caused by chemotherapy for patients with breast carcinoma in community practice settings. Cancer. Jul 1; 1999 86(1):64–71. [PubMed: 10391565]
4. Holdsworth MT, Raisch DW, Frost J. Acute and delayed nausea and emesis control om pediatric oncology patients. Cancer. 2006; 106(4):931–340. [PubMed: 16404740]
5. De Mulder PH, Seynaeve C, Vermorken JB, et al. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. A multicenter, randomized, double-blind, crossover study. Ann Intern Med. Dec 1; 1990 113(11):834–840. [PubMed: 2146911]
6. Latreille J, Pater J, Johnston D, et al. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. Mar; 1998 16(3):1174–1178. [PubMed: 9508205]
7. Morrow GR, Hickok JT, Rosenthal SN. Progress in reducing nausea and emesis. Comparisons of ondansetron (Zofran), granisetron (Kytril), and tropisetron (Navoban). Cancer. Aug 1; 1995 76(3): 343–357. [PubMed: 8625113]
8. Herrstedt J, Dombernowsky P. Anti-emetic therapy in cancer chemotherapy: current status. Basic Clin Pharmacol Toxicol. Sep; 2007 101(3):143–150. [PubMed: 17697032]
9. Lee J, Dodd M, Dibble S, Abrams D. Review of Acupressure Studies for Chemotherapy-Induced Nausea and Vomiting Control. Journal of Pain and Symptom Management. November; 2008 36(5): 529–544. [PubMed: 18440769]
10. Ryan JL, Heckler C, Dakhil SR, et al. Ginger for chemotherapy-related nausea in cancer patients: A URCC CCOP randomized, double-blind, placebo-controlled clinical trial of 644 cancer patients. Journal of Clinical Oncology. 2009; 27(15s) suppl abstr 9511.
11. Herrstedt J. Antiemetics: an update and the MASCC guidelines applied in clinical practice. Nature Clinical Practice Oncology. January; 2008 5(1):32–43.
12. Brearley SG, Clements CV, Molassiotis A. A review of patient self-report tools for chemotherapy-induced nausea and vomiting. Support Care Cancer. Nov; 2008 16(11):1213–1229. [PubMed: 18551323]
13. Hickok JT, Roscoe JA, Morrow GR, King DK, Atkins JN, Fitch TR. Nausea and emesis remain significant problems of chemotherapy despite prophylaxis with 5-Hydroxytryptamine-3 antiemetics. Cancer. June 1; 2003 97(11):2880–2886. [PubMed: 12767103]
14. Quimby EL. The use of herbal therapies in pediatric oncology patients: treating symptoms of cancer and side effects of standard therapies. J Pediatr Oncol Nurs. Jan-Feb; 2007 24(1):35–40. [PubMed: 17185400]
15. Roscoe JA, Bushunow P, Morrow GR, et al. Patient expectation is a strong predictor of severe nausea after chemotherapy. Cancer. December 1; 2004 101(11):2701–2708. [PubMed: 15517574]
16. Jacobsen PB, Bovbjerg DH, Redd WH. Anticipatory anxiety in women receiving chemotherapy for breast cancer. Health Psychol. Nov; 1993 12(6):469–475. [PubMed: 8293730]
17. Morrow, GR.; Roscoe, JA. Anticpatory nausea and vomiting: Models, mechanisms and management. In: Dicato, M. e, editor. Medical management of cancer treatment induced emesis. Martin Dunitz; London: 1997. p. 149-166.

18. Dupuis LL, Lau R, Greenberg ML. Effectiveness of strategies for the prevention of cute neoplastic-induced nausea and vomiting in children receiving antineoplastic agents. Pharmacotherapy. 1999; 26(9):1221–1231. [PubMed: 16945043]
19. Tyc VL, Mulhern RK, Bierberich AA. Anticipatory nausea and vomiting in pediatric cancer patients: an analysis of conditioning and coping variables. J Dev Behav Pediatr. 1997; 18:27–33. [PubMed: 9055147]
20. Figueroa-Moseley C, Jean-Pierre P, Roscoe JA, et al. Behavioral interventions in treationg anticipatory nausea and vomiting. J Natl Compr Canc Netw. 2007; 5(1):44–50. [PubMed: 17239325]
21. Morrow GR, Dobkin PL. Anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment: Prevalence, etiology, and behavioral interventions. Clinical Psychology Reviews. 1988; 8:517–556.
22. Morrow GR, Roscoe JA, Hickok JT, Andrews PR, Matteson S. Nausea and emesis: evidence for a biobehavioral perspective. Support Care Cancer. Mar; 2002 10(2):96–105. [PubMed: 11862499]
23. Morrow GR, Roscoe JA, Hickok JT, Banerjee TK, Issel B, Kirshner JJ. Time of first occurrence, severity, and persistence of nausea following initial chemotherapy in 322 patients: A URCC CCOP study. Supportive Care in Cancer. 2001; 9:290.
24. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer. 2004; 100:2261–2268. [PubMed: 15139073]
25. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. Ann Pharmacother. 2005; 39:77–85. [PubMed: 15562136]
26. Shukla Y, Singh M. Cancer preventive properties of ginger: a brief review. Food Chem Toxicol. May; 2007 45(5):683–690. [PubMed: 17175086]
27. Natural Health Bible: From the most trusted source in health information, here is your A-Z guide to over 200 herbs, vitamins, and supplements. Prima Publishing; Roseville, CA: 1999.
28. Arfeen Z, Owen H, Plummer JL, Ilsley AH, Sorby-Adams RA, Doecke CJ. A double-blind randomized controlled trial of ginger for the prevention of postoperative nausea and vomiting. Anaesth Intensive Care. Aug; 1995 23(4):449–452. [PubMed: 7485935]
29. Bone ME, Wilkinson DJ, Young JR, McNeil J, Charlton S. Ginger root--a new antiemetic. The effect of ginger root on postoperative nausea and vomiting after major gynaecological surgery. Anaesthesia. Aug; 1990 45(8):669–671. [PubMed: 2205121]
30. Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol. Jan 4; 1991 38(1):19–24. [PubMed: 1988321]
31. Grontved A, Brask T, Kambskard J, Hentzer E. Ginger root against seasickness. A controlled trial on the open sea. Acta Otolaryngol. Jan-Feb; 1988 105(1-2):45–49. [PubMed: 3277342]
32. Mowrey DB, Clayson DE. Motion sickness, ginger, and psychophysics. Lancet. Mar 20; 1982 1(8273):655–657. [PubMed: 6121968]
33. Phillips S, Ruggier R, Hutchinson SE. Zingiber officinale (ginger)--an antiemetic for day case surgery. Anaesthesia. Aug; 1993 48(8):715–717. [PubMed: 8214465]
34. Visalyaputra S, Petchpaisit N, Somcharoen K, Choavaratana R. The efficacy of ginger root in the prevention of postoperative nausea and vomiting after outpatient gynaecological laparoscopy. Anaesthesia. May; 1998 53(5):506–510. [PubMed: 9659029]
35. Zick SM, Ruffin MT, Lee J, et al. Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting. Support Care Cancer. May; 2009 17(5):563–572. [PubMed: 19005687]
36. Pace, JC. Oral ingestion of encapsulated ginger and reported self-care actions for the relief of chemotherapy-associated nausea and vomiting: Nursing. University of Alabama; 1986.
37. Meyer K, Schwartz J, Crater D, Keyes B. Zingiber officinale (ginger) used to prevent 8-Mop associated nausea. Dermatol Nurs. Aug; 1995 7(4):242–244. [PubMed: 7646942]
38. Sontakke S, Thawani V, Naik MS. Ginger as an antiemetic in nausea and vomiting induced by chemotherapy: A randomized, cross-over, double-blind study. Indian Journal of Pharmacology. 2003; 35(1):32–36.

39. Levine ME, Gillis MG, Koch SY, Voss AC, Stern RM, Koch KL. Protein and ginger for the treatment of chemotherapy-induced delayed nausea. J Altern Complement Med. Jun; 2008 14(5): 545–551. [PubMed: 18537470]

40. Ezzo J, Vivkers A, Richardson MA, et al. Acupuncture-Point Stimulation for Chemotherapy-Induced Nausea and Vomiting. Journal of Clinical Oncology. October 1; 2005 23(28):7188–7198. [PubMed: 16192603]

41. ProStraken. http://www.sancuso.com

42. Tan L, Liu J, Liu X, et al. Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. Journal of Experimental and Clinical Cancer Research. 2009; 28:131.