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current trial

A Phase II/III Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Ginger (*Zingiber officinale*) for Nausea Caused by Chemotherapy for Cancer: A Currently Accruing URCC CCOP Cancer Control Study

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Abstract

Despite the widespread use of 5-HT_3 receptor antagonist antiemetics such as ondansetron and granistron, up to 70% of patients with cancer receiving highly emetogenic chemotherapy agents experience postchemotherapy nausea and vomiting. Delayed postchemotherapy nausea (nausea that occurs ≥ 24 hours after chemotherapy administration) and anticipatory nausea (nausea that develops before chemotherapy administration, in anticipation of it) are poorly controlled by currently available antiemetic agents. Scientific studies suggest that ginger (*Zingiber officinale*) might have beneficial effects on nausea and vomiting associated with motion sickness, surgery, and pregnancy. In 2 small studies of patients with cancer receiving chemotherapy, addition of ginger to standard antiemetic medication further reduced the severity of postchemotherapy nausea. This article describes a phase II/III randomized, dose-finding, placebo-controlled, double-blind clinical trial to assess the efficacy of ginger for nausea associated with chemotherapy for cancer. The study is currently being conducted by private practice oncology groups that are funded by the National Cancer Institute's Community Clinical Oncology Program and affiliated with the University of Rochester Cancer Center Community Clinical Oncology Program Research Base.

Introduction

Despite the widespread use of 5-HT_3 receptor antagonist antiemetics such as ondansetron, granistron, and dolasetron mesylate, postchemotherapy nausea and vomiting continue to be experienced by up to 70% of patients receiving highly emetogenic chemotherapy agents, such as cisplatin, carboplatin, and doxorubicin.[1] Research also suggests that the 5-HT_3 receptor antagonists are clinically more effective against emesis than they are against nausea.[2]

Delayed postchemotherapy nausea (nausea that occurs ≥ 24

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Ginger for Nausea of Chemotherapy

hours after chemotherapy administration) and anticipatory nausea (nausea that develops before chemotherapy administration, in anticipation of it) are poorly controlled by currently available antiemetic agents. Data from a previously completed University of Rochester Cancer Center Community Clinical Oncology Program (CCOP) Research Base study of patients receiving cisplatin, carboplatin, or doxorubicin showed that 77% of 691 patients experienced delayed nausea and indicated that, whereas nausea was most likely to develop within the first 48 hours after administration of chemotherapy, it was first reported on or after day 3 of the cycle in 18% of the patients.[3] Furthermore, 20%-30% of patients who have chemotherapy nausea after chemotherapy develop anticipatory nausea or vomiting, which are also resistant to pharmacologic treatment.[3-6] Antiemetics in widespread use can be associated with significant adverse effects, such as sedation, extrapyramidal side effects, and hypotension (dopamine antagonists), and headache, diarrhea, or constipation (5-HT_3 receptor antagonists). There is still a great deal of room for improvement in the control of nausea and vomiting associated with chemotherapy for cancer.

Rationale

Ginger (*Zingiber officinale*), an ancient spice, is best known for its role as a flavoring agent for food in Asian and Indian recipes. Since the 16th century, the dried aromatic rhizome (underground stem) of ginger has been used by practitioners of 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 in Germany. Scientific studies have suggested that ginger might have beneficial effects on nausea and vomiting associated with motion sickness,[7,8] surgery,[9,10] and pregnancy.[11,12] In 2 small studies of patients with cancer receiving chemotherapy, the addition of ginger to a standard antiemetic medication further reduced the severity of postchemotherapy nausea.[13,14]

Although previous research suggests that ginger might be effective against nausea associated with chemotherapy, design inadequacies and small numbers limit the power and generalizability of the results. Dosages used in published studies have varied widely, and no dose-response studies have been reported. We are currently conducting a phase II/III randomized, dose-finding, placebo-controlled, double-blind clinical trial to assess the efficacy of ginger for nausea associated with chemotherapy for cancer in the private practice oncology groups funded by the National Cancer Institute's CCOP and affiliated with the University of Rochester Cancer Center CCOP Research Base. The primary objective is to determine whether ginger is more effective than placebo in controlling chemotherapy-related nausea when added to an antiemetic regimen of a 5-HT_3 receptor antagonist plus dexamethasone (or the equivalent dose of intravenous methylprednisolone) on day 1 of chemotherapy. Secondary objectives are to determine the most effective dose (0.5 g, 1 g, or 1.5 g daily for 6 days) of ginger, to identify adverse effects of ginger, to determine the effectiveness of ginger against anticipatory nausea, and to determine if ginger is more effective than placebo in maintaining participants' quality of life during the 4 days immediately after chemotherapy. Innovative aspects of our study design include collecting baseline data on nausea after the first cycle of chemotherapy; beginning the intervention 3 days before chemotherapy (as suggested for relief of motion sickness) to maximize the postchemotherapy effect of ginger; assessing symptoms before taking any ginger, after 3 days of ginger alone, and after 3 days of ginger plus standard antiemetics at the 2 chemotherapy cycles after the measurement of nausea at the baseline chemotherapy cycle, assessing anticipatory nausea, as well as acute and delayed postchemotherapy nausea, and using validated measures for outcome assessment. The primary outcome is the assessment of nausea after 1 chemotherapy cycle with the intervention (study cycle 2). We continue the intervention for an additional cycle of chemotherapy (study cycle 3) to assess the consistency of any effectiveness of ginger for nausea as an exploratory analysis.

Criteria

Ginger is listed as a food on the Food and Drug Administration's "generally recognized as safe" list. Although the pharmacology of ginger has not been studied extensively in humans and the mechanism of action by which ginger might reduce nausea/vomiting is not completely known, its aromatic, antispasmodic, and carminitive (relief of flatulence) properties suggest that it might act directly on the gut itself rather than centrally to reduce these symptoms.[8,15,16] Adverse clinical symptoms are uncommon; heartburn, nausea, or flatulence have been experienced by a small number of patients.[17] Although some in vitro experiments have shown inhibition of platelet aggregation,[18] no in vivo studies have confirmed these findings in the doses of ginger used in this study.[19-21]

The dose of ginger contained in each capsule is 250 mg. Ginger gelatin capsules are standardized with 1.5 wt % combined gingerols, zingerone, and shogaol content. The use of excipients such as soybean oil (> 90%) and a flavoring agent masks some of the smell and taste and makes the placebo