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Searching for Evidence to Support the Use of Ginger in the Prevention of Chemotherapy-Induced Nausea and Vomiting

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Abstract

Patients with cancer frequently use dietary supplementation and herbal therapies to control symptoms of disease and adverse effects of cancer therapy. Despite the widespread use of dietary supplementation and herbal therapies in oncology, robust scientific evidence in this area is lacking. Not only do these products need to be tested in large and well-designed observational or randomized studies, but their manufacturing process must be improved to achieve higher levels of standardization in product quality. Ginger is frequently used to counteract chemotherapy-induced nausea and vomiting (CINV), and some suggestions that it might be effective against CINV come from randomized and/or crossover clinical trials. However, several limitations in the methods of these studies limit their power and generalizability. The authors are conducting a randomized, double-blind study with a large sample size and homogeneous inclusion criteria in order to evaluate the efficacy of a well-standardized ginger extract in reducing nausea in patients with cancer. The widespread use of standardized herbal therapies and natural components among patients requires that scientific and rigorous research strategies are applied in this field to guide the physicians and the patients in safer use.

Introduction

The use of dietary supplementation and herbal therapies has become highly prevalent among patients with cancer.[1] Up to 80% of cancer survivors take vitamin and mineral supplements, and 14%–32% of patients begin using supplements after they are diagnosed with cancer.[2] These interventions may help control symptoms of disease and the adverse effects of cancer therapy, such as nausea, vomiting, and oral mucositis.[3] A potential role of these interventions in the prevention of different types of cancer has also been suggested; however, although some isolated evidence led to promising results,[4] at present their use in the primary prevention of chronic diseases, including cancer, cannot be recommended.[5] In addition, the uncontrolled use of these therapies may result in increased costs.[6]

Despite the widespread use of nutritional supplements and herbal therapy in oncology, only a few of these intervention have been evaluated with scientific research tools.[7,8] A major gap exists between the current level of scientific evidence and what is needed to provide robust, evidence-based advice.[7] Research is limited by a lack of sufficient funding and qualified investigators, as well as by methodological and ethical issues. Therefore, ''gaps in research are the norm rather than the exception in this field,'' according to the Society for Integrative Oncology.[7] The performance of large and well-designed observational or randomized studies—likely with the support of government institutions or pharmaceutical companies—will identify well-grounded evidence on the potential benefits and risks of these complementary therapies, with substantial effects on personal and clinical decision-making and policy-making.[7,8]

Nevertheless, to reduce the overall bias of clinical results, it is of primary importance to improve product quality. This methodological aspect is necessary for herbals, for which

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the relative concentration of active substances in each single preparation can vary significantly, with direct variation of clinical results. The results will therefore reflect this bias even if the clinical trial is conducted according to large and well-designed observational or randomized studies. Modern technologies to standardized the product should therefore be used.[9,10]

The use of complementary treatment substances is particularly intriguing in the prevention of adverse events due to oncologic treatment. In this regard, chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing symptoms.[11,12]

This article discusses ginger as an example. Ginger (*Zingiber officinale*) has been used for centuries as a remedy for many gastrointestinal conditions.[13] Its use in this setting is justified by its chemical properties. The rhizome of ginger possesses an array of bioactive compounds, such as gingerols, shogaols, zingiberene, zingerone, and paradol, that may stimulate oral and gastric secretions, regulate gastrointestinal motility, interact with the 5HT3 and NK1 receptors involved in the CINV reflex, and act as a scavenger for free radicals.[13] Common side effect are heartburns and dermatitis; sometimes heartburn onset can be confused with nausea persistence.[14]

A recent systematic literature review[15] identified seven randomized and/or crossover trials of ginger versus placebo or current antiemetic therapies in patients undergoing chemotherapy.[16–22] The sample sizes of these studies ranged from 36 to 576 patients, who were receiving a variety of chemotherapy regimens. The timeframe of CINV symptom assessment varied among the studies from 3 days before chemotherapy treatment to 10 days after treatment. In most cases, ginger was supplied as encapsulated powder or standardized extracts based on gingerol content. Dosing was 1–2 g per day over 1–10 days. Overall, three trials demonstrated the benefit of ginger in the management of acute or delayed CINV,[19–21] two showed an effect similar to that of metoclopramide,[17,18] and two had unsatisfactory results.[16,22] Moreover, the heterogeneity of ginger doses and formulations, and often the lack of appropriate antiemetic treatment in the control group, limit the applicability of these results to daily clinical practice.

Globally, suggestions that ginger might be effective against CINV exist, but design inadequacies, heterogeneity of the patient population, small numbers, and lack of dose-finding studies limit the power of the trials and the possibility to offer generalized results.

The authors have launched a randomized, double-blind, placebo-controlled, clinical trial in six Italian centers with two parallel groups of patients receiving at least two cycles of highly emetogenic treatments (ClinicalTrials.gov identifier: NCT01887314). The study was approved by the ethics committee of the Istituto Nazionale Tumori and by the ethics committees of all the other centers involved in the study. All patients signed an informed consent form before inclusion in the trial. The patients are randomly assigned to treatment with 160 mg of ginger extract per day (Ginpax [Helsinn Healthcare SA, Lugano, Switzerland], soft-gel capsules; ginger is grown in China and then is submitted to a strict surveillance of each batch of product with repeated analyses aimed at characterizing the ingredients) or to placebo between day 2 of cisplatin-based chemotherapy and the day before the next cycle. All patients receive the standard prophylaxis against cisplatin-induced acute (aprepitant, dexamethasone and a 5-HT3 antagonist) and delayed (aprepitant plus dexamethasone) emesis.

The primary objective of this study is to evaluate the efficacy of a well-standardized ginger extract, containing a fixed amount of gingerols and shogaols, in reducing delayed nausea in patients with cancer over two cycles of highly emetogenic treatments. In more detail, the main endpoint is to evaluate the protection from delayed nausea; secondary endpoints include overall duration and severity of nausea, intercycle nausea, and nausea anticipatory symptoms. Safety considerations will be taken, and the potential correlation of treatment-emerging adverse events with the study product will be assessed. On the basis of literature review, the sample size was estimated to be 250 patients in order to have a sample large enough to assess a difference of 15% between the two treatment groups in the proportion of patients with no nausea. This large sample size, the strict and homogeneous inclusion criteria, and the double-blind design are the principal strengths of this study. Moreover, a translational part is foreseen, aimed at identifying the level of serum inflammatory cytokines in a subgroup of patients.

Complementary and alternative medicines are largely diffused throughout the world, and their use has rapidly grown in recent years.[1,2,16,17] However, not all these compounds are harmless, and the perception of safe and holistic treatment could expose patients to uncontrolled use.

Because of the widespread use of standardized herbal therapies and natural components among patients, scientific and rigorous research strategies are necessary. Also needed is knowledge of the benefits and possible harms or interactions of complementary medicine in supportive care. The scientific method should be maintained consistently in this field in order to provide evidence-based recommendations that can guide physicians and patients in safer use and make them aware of the real benefit of these agents, their potential interactions with other drugs, and adverse events.

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Author Disclosure Statement

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