Commentary

We need well-grounded evidence to support complementary medicine in cancer supportive care: the case of Ginger for the prevention of CINV

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The use of dietary supplementation and herbal therapies has become highly prevalent among cancer patients [1]. It has been shown that up to 80% of cancer survivors take vitamin and mineral supplements, and that 14% to 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, but, 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, even the major scientific societies of the field state that 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*", as stated by the Society for Integrative Oncology [7]. The conduction of large and well-designed observational or randomized studies – likely with the support of government institutions or pharma companies - will allow the identification of well-grounded evidence on the potential benefits and risks related with taking these complementary therapies, with substantial effects on personal and clinical decision-making and policy making [7,8].

Nevertheless, it is of primary importance, in order to reduce the overall bias of clinical results, to work on the product quality. This methodological aspect is of primary importance in particular for herbals. In fact, when a "natural" form (i.e. dried and or grinder parts of plants) is used, 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].

Ginger (*Zingiber officinale*) has been used for centuries by many cultures as a remedy for a number of gastrointestinal-related conditions [13]. The use of ginger 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 acting as a scavenger for free radicals [13]. Common side effect are heartburns and dermatitis; sometimes heartburns onset can be confused with nausea persistence [14].

In a recent systematic literature review, seven randomized and/or crossover trials of ginger versus placebo or current antiemetic therapies in patients undergoing chemotherapy were identified [15]. The sample sizes of these studies ranged from 36 to 576 patients, who were on a variety of chemotherapy regimens. In most cases, ginger was supplied as encapsulated powder or standardized extracts based on gingerol content. Dosing was 1 to 2 g per day over 1 to 10 days. Overall, three trials demonstrated the benefit of Ginger in the management of CINV, two showed an effect comparable with that of metoclopramide, and two studies led to not satisfactorily results. Moreover, heterogeneity of ginger doses and formulations, and often

lack of appropriate antiemetic treatment in the control arm, make these results hardly applicable to daily clinical practice.

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

We started in six Italian Centers a randomized, double-blind, placebo controlled, clinical trial with two parallel groups of patients receiving at least 2 cycles of highly emetogenic treatments (*ClinicalTrials.gov identifier: NCT01887314*). The patients are randomly assigned to treatment with either 160 mg/day of Ginger extract or to placebo, since day 2 after cisplatin-based chemotherapy to the day before the further cycle. All patients receive the standard prophylaxis for 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 cancer patients over two cycles of highly emetogenic treatments. The large sample size (250 patients), 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 is rapidly growing in the last years [1,2,16,17]. However, not all these compounds are harmless and the perception of safe and holistic treatment could expose the patients to an uncontrolled use.

We believe that the widespread use of standardized herbal therapies and natural components among the patients need scientific a rigorous research strategies. The knowledge about the

benefits and the possible harms or interaction of complementary medicine in supportive care is needed. The scientific method should be maintained consistently in this field, in order to provide evidence-based recommendations able to guide the physicians and the patients in a safer use, well aware of the real benefit of these agents, the potential interactions with other drugs and the adverse events.

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