Complementary therapies for side effects of chemotherapy and radiotherapy in the upper gastrointestinal system

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Abstract

Introduction: Chemotherapy and radiotherapy remain the mainstay of treatment for patients with advanced malignant disease that is incurable by local surgery. However, effective use of these therapies is limited by toxic effects. Serious side effects in the upper GI system include mucositis, xerostomia, nausea and vomiting. Standard care for these side effects is suboptimal. Recent studies suggest complementary and alternative medicine (CAM) may have a role in supportive care for people with cancer. We therefore reviewed the literature to assess the potential role of CAM in upper GI toxicities of chemo/radiotherapy.

Methods: We conducted a Medline term-combination search for articles in English that included: stomatitis, mucositis, xerostomia, nausea, vomiting, chemotherapy, radiotherapy, complimentary/alternative therapies, amino acids, antioxidants, vitamins, minerals, plant extracts, herbs, mind–body, guided imagery, hypnosis, acupuncture, massage and yoga.

Results: The initial search identified a total of 217 articles. Of these, 36 were selected and reviewed. Recommendations for integration of some CAM therapies in supportive cancer care can be made.

Conclusion: CAM therapies can be effective and safe in treating upper GI toxicities of chemo/radiotherapy. Guidelines in supportive cancer care should include appropriate CAM therapies, and patients need to be informed of such treatment options.

Keywords: Stomatitis; Mucositis; Xerostomia; Nausea; Vomiting; Chemotherapy; Radiotherapy; Complementary and alternative medicine

Introduction

Upper alimentary tract toxicity can be a serious complication of chemotherapy and radiotherapy [1], mucositis, xerostomia, nausea and vomiting being the most common of them. Current supportive care does not offer optimal treatment for these side effects. In recent years there has been a growing body of literature that documents the benefits of several complementary and alternative medicine (CAM) therapies in supportive cancer care. In this article we will summarize our findings from a literature review on CAM therapies with positive outcomes for upper GI side effects of radio/chemotherapy.

Methods

The authors independently searched Pubmed for keywords (alone and in various combinations) in the following categories:

a. Oncology-related keywords (cancer; oncology; palliative; chemotherapy; radiation).

b. CAM-related keywords (CAM, complementary/alternative/integrative medicine, integrative oncology, traditional medicine, herbs, herbal, mind–body, relaxation, meditation, guided imagery, hypnosis, homeopathy, acupuncture, nutritional/dietary supplements, naturopathy, energy, healing, manual healing, massage, reflexology, yoga, Alexander, Feldenkrais, and anthroposophic medicine).

c. Keywords related to upper gastro-intestinal symptoms: nausea, vomiting, xerostomia, mucositis, and aphthous stomatitis.
The initial search identified a total of 217 articles. Of these, 36 articles focusing on the clinical practice of CAM in gastrointestinal symptoms during active oncology treatment were selected and reviewed.

**Chemotherapy and radiotherapy induced mucositis**

Cytotoxic chemotherapies and radiotherapies are most effective against rapidly dividing cells. However, a negative consequence of this mechanism is that host tissues containing rapidly dividing cells may be damaged. The cells of the GI tract are the most rapidly proliferating cells in the human body; hence they are prone to such toxicity. Oral mucositis, i.e. inflammation of the mucous membrane lining the mouth, is a common dose-limiting toxic effect of chemotherapy, especially fluoropyrimidines, anthracyclines, and folate-based drugs such as methotrexate [2]. Oral mucositis is associated with a higher risk of infection, pain, chemotherapy-dose reduction, and infection-related death. Furthermore, severe mucositis commonly results in compromised nutritional intake and quality of life. At present, there is no standard therapy to prevent mucositis [1]. Treatment is mostly supportive, consisting of good oral hygiene, mouthwashes, and analgesia [3].

**Herbal and nutritional approaches to mucositis**

Honey was a traditional remedy used to treat wounds until the introduction of antibiotics. Honey has been shown to inhibit bacterial growth and enhance wound healing [4]. Three trials have evaluated the role of honey for the prevention of chemo/radiotherapy induced mucositis. In a double blind randomized clinical trial from Iran, patients took 20 ml of honey (swish & swallow) 15 min before, 15 min after, and 6 h after radiotherapy [5]. Compared to saline rinse a significant reduction in mucositis severity was observed among patients in the honey-treated group. In another randomized trial from Egypt, honey rinse prophylaxis was also shown to significantly reduce mucositis severity in head and neck cancer patients receiving either chemotherapy or radiotherapy [6]. In another trial from Malaysia, a significant reduction in mucositis was observed among prophylactic honey-treated patients compared to controls. In addition, 55% of patients treated with topical honey showed no change or a positive gain in body weight compared to 25% in the control arm, the majority of whom lost weight [7].

Chinese herbs are an essential part of the healthcare system in several Asian countries, and are considered to be CAM in most Western countries. Although Chinese herb consumption is becoming increasingly popular the evidence base of this field is still in its infancy. Moreover, issues of safety are significant, especially in terms of herb-drug interactions. Two RCT’s reported the efficacy of Chinese herbal formulas for prevention of chemo/radiotherapy-induced mucositis in 395 patients with head and neck cancer. The herbal formulas were individualized according to traditional Chinese medical diagnosis. Each formula contained a mixture of more than five herbs. Patients in the control group received Dobell’s solution (an antiseptic mouthwash solution) [8,9]. Chinese herbs showed a benefit at all mucosal injury levels with risk reduction values ranging between 0.16 and 0.59. A Cochrane review concluded that Chinese herbs were found to have some benefit in preventing or reducing the severity of mucositis associated with cancer treatment [3].

Syousai-kotou, a Japanese herbal preparation was compared to gargling with providone-iodine and amphotericin B, in patients undergoing chemotherapy [10]. Syousai-kotou significantly reduced both the incidence of mucositis and the pain associated with such lesions. The analgesic effects of Syousai-kotou gargle lasted for about 2 h. No major adverse effects were noted in the herbal preparation group.

**Dietary and homeopathic supplements in the treatment of mucositis**

L-Glutamine is a conditionally essential amino acid that has multiple well-defined functions in human biological processes. Several studies have evaluated the role of glutamine for the prevention and treatment of chemo/radiotherapy-induced mucositis. Although trials vary in methodology, glutamine formulation and dosing, there is sufficient evidence for effectiveness and safety to support its use in the treatment of stomatitis [11,12].

Saforis is a proprietary oral glutamine formula that facilitates delivery of glutamine into oral mucosal cells. In a double blind randomized control trial, Saforis significantly reduced the incidence of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy [13]. No significant adverse effects occurred in the Saforis group. Further trials are needed to establish the role of glutamine for prevention of oral mucositis.

Alpha-Tocopherol, a form of the antioxidant vitamin E, was assessed for the prevention of mucositis. Patients receiving radiotherapy for cancer of the oropharynx were randomized to Alpha-Tocopherol mouth rinse or placebo. Patients rinsed their mouths before each radiation treatment, and again 8–12 h later. Alpha-Tocopherol was associated with a 12.9% reduction in mucositis incidence as well as a 41.1% reduction in mucositis severity [14]. Although the issue of antioxidant consumption during radiotherapy remains controversial, in this trial no survival difference was observed between groups.

Traumeel is a homeopathic-complex remedy. In one laboratory study, Traumeel was shown to inhibit the secretion of pro-inflammatory mediators from gut epithelial cells in an inversely dose-related manner. Interestingly, these mediators are considered to play a role in generating mucosal inflammation [15]. In a double-blind controlled trial, 32 patients undergoing allogeneic or autologous stem cell transplantation were randomized to receive either Traumeel or placebo as a mouth rinse for the prevention and treatment of stomatitis. In the Traumeel group patients developed significantly less stomatitis, and lesions were less severe [16]. However, in a trial that ended only recently, Traumeel was not superior to placebo in preventing or treating mucositis in young patients undergoing stem cell transplantation [17]. Another trial for assessing Traumeel for radiation-induced mucositis is currently being conducted.
Mind–body approaches to mucositis treatment

Psychological interventions are important in the context of supportive care for people with cancer. In one trial, patients receiving bone marrow transplantation were given either therapist support, or relaxation and imagery training, or cognitive-behavioral coping skills with relaxation and imagery, or placebo control for the management of mucositis-related pain. Patients who received either relaxation and imagery alone, or the package of cognitive-behavioral coping skills with added relaxation and imagery, reported significantly less pain compared with patients in the other groups. Cognitive-behavioral skills were not more beneficial than relaxation and imagery alone, suggesting relaxation and imagery training, whether by itself or in conjunction with cognitive skills, reduces cancer treatment-related mucositis [18].

Radiation-induced xerostomia

Radiation to the head and neck area results in injury to salivary glands, eventually leading to little or no saliva production. The extent of reduction in salivary flow depends on the radiation dose and fractional size, as well as the volume of salivary glands irradiated [19]. Up to 100% of patients receiving radical radiotherapy develop some degree of xerostomia, the subjective sensation of dryness of the mouth. They also may have oral discomfort and pain, greatly increased susceptibility to dental caries, frequent oral infections, and difficulty in speaking, chewing, and swallowing. These outcomes can lead to severe oral disease, nutritional deficiencies, and an overall decline in quality of life [20]. There are few treatment options for alleviating xerostomia in these patients. Salivary substitutes and sialogogues, such as pilocarpine [21] are often tried, as well as submandibular gland transfer [22]. These treatment modalities have shown varying degrees of effectiveness and diverse side effects. Consequently, xerostomia continues to have a substantial negative impact on the quality of life of survivors of head and neck cancer [23].

Acupuncture in the treatment of xerostomia

Acupuncture has gained significant momentum in current research, after reports of successful palliation of xerostomia appeared in the West as early as 1992 [24]. Promising preliminary data were reported from a group of patients with strictly defined pilocarpine-resistant radiation-induced xerostomia [25]. Blom and Lundeborg found that 24 acupuncture treatments resulted in statistically significant improvement in the salivary flow rate (SFR) in patients with xerostomia in the long term, up to 6 months, and noted that additional acupuncture treatments can maintain this improvement in SFR for up to 3 years [26]. Other investigators have reported equally promising results using noninvasive transcutaneous electrical nerve stimulation (TENS) of acupuncture points with either traditional TENS or the newer proprietary Codetron technique [27]. However, this acupuncture-like TENS device was not superior to standard care in preventing the development of xerostomia [28]. In a recent trial, acupuncture produced greater improvement than usual care in xerostomia, as well as in pain and dysfunction, in patients with cancer and a history of neck dissection [29]. In another feasibility trial, a standardized acupuncture group technique was shown to be deliverable and effective [30], thereby reducing treatment cost.

Acupuncture may exert its effects on salivary flow through multiple mechanisms. fMRI studies have been used to evaluate specificity of acupuncture stimulation on neuronal activity. In a recent fMRI study, unilateral manual acupuncture stimulation at LI-2, a point commonly used in clinical practice to treat xerostomia, was associated with bilateral activation of the insula and adjacent operculum-areas in the brain that modulate salivation. Sham acupuncture at an adjacent site induced neither activation nor deactivation. True acupuncture also induced more saliva production than sham acupuncture [31].

Hypnosis and xerostomia

In a pilot study, Schiff et al. evaluated the effect of hypnosis on radiation-induced xerostomia and salivary flow rates [32]. Twelve patients received a single hypnosis session with specific suggestions to increase salivation. The session was recorded on a compact disk, and the participants were instructed to listen to it twice a day for 1 month. A substantial overall improvement was reported by eight patients at 12 weeks (66%). The salivary flow rate increased on sialometry in nine patients following hypnosis (75%). Symptomatic improvement significantly correlated with the number of times the patients listened to the hypnosis CD. No adverse events were reported. In a follow-up qualitative study, a focus group from the above 12 patients reported that following the hypnosis session they improved their quality of life and felt more in control of their lives [33]. Confirmation of results in a larger randomized and controlled investigation is warranted.

Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting are some of the most distressing side-effects of cancer treatment [34]. Before the use of modern antiemetics, patients ranked nausea and vomiting as the most distressing toxic effects of systemic chemotherapy [35]. To date, chemotherapy-induced emesis continues to negatively affect quality of life and can deter patients from continuing treatment [36]. Nausea and vomiting associated with chemotherapy can be acute, delayed, or anticipatory. Chemotherapy-associated emesis is divided into acute (within 24 h of treatment), delayed (occurring more than 24 h after treatment for up to 1 week), and anticipatory emesis which occurs before chemotherapy in patients with poorly controlled emesis from a previous course of chemotherapy. The severity and pattern of chemotherapy-induced emesis depends on several factors associated with the patient as well as on the type of chemotherapy, dose schedule, and regimen.

Prevention of acute emesis is based on the combination of 5-hydroxytryptamine-3 receptor (5-HT3R) antagonists combined with oral dexamethasone [37]. Corticosteroids are recommended for prevention of delayed symptoms, combined with...
metoclopramide or 5-HT3R antagonists. Use of 5-HT3R antagonists and dexamethasone results in total prevention of acute emesis in 65–80% of patients [38]. However, many patients will not achieve emetic control, which has led to the development of newer therapies such as Aprepitant, a protonchymkin-1 receptor antagonist. Many CAM therapies have been evaluated for chemotherapy-induced nausea and vomiting. The following have shown promising effects.

**Massage and nausea relief**

Massage has been shown to relieve pain and nausea and relax hospitalized patients with cancer [39,40]. Billhult et al. evaluated the effect of massage on nausea, anxiety, and depression in patients with breast cancer undergoing chemotherapy [41]. In this prospective, randomized, controlled trial, 39 women with breast cancer undergoing chemotherapy were randomly assigned to a massage therapy group (20 min of massage on five occasions) or an attention control group (five 20-min visits). Massage treatment significantly reduced nausea compared with control treatment. In a more recent study [42], the impact of therapeutic massage on the quality of life of patients undergoing treatment for breast cancer was assessed by measuring anxiety, pain, nausea, sleep quality, and quality of life. Massage treatment consisted of one 30-min treatment per week for 3 consecutive weeks. Enhanced quality of life was reported to occur as early as after 3 weeks of massage therapy. Furthermore, alleviation of anxiety and sleep quality significantly improved too. Among study participants, there was variability in reported episodes of nausea, vomiting, and retching; although participants reported decreased pain and distress, changes were insignificant. The results of these trials are encouraging, however, firm recommendations cannot be provided due to the small sample size.

**Acupuncture treatment for nausea and vomiting**

Ezzo et al. conducted a systematic review and meta-analysis of acupuncture for chemotherapy-induced nausea and vomiting [43]. The pooled results of their analysis showed a significant reduction in the proportion of patients experiencing acute nausea and vomiting. In a sub-group analysis of different modes of acupuncture delivery it appeared that stronger forms of stimulation, such as electroacupuncture were more effective than acupressure. Acupuncture did not show effectiveness for delayed nausea and vomiting. Noninvasive electrostimulation, too, appeared to offer no benefit for any measurable outcomes. Importantly, acupuncture was found to be safe for patients undergoing chemotherapy. There have been no trials that specifically assess acupuncture for anticipatory nausea and vomiting. However, inference may be suggested from studies of anticipatory nausea in other circumstances [44].

**Mind–body intervention for nausea**

Several mind–body techniques have been evaluated for the treatment of chemotherapy-induced nausea and vomiting. Richardson et al. conducted a systematic review on hypnosis for chemotherapy-induced nausea and vomiting [45]. Six RCT’s (five of them in a pediatric population) were available for final analysis. Studies were heterogeneous regarding timing and content of the hypnosis intervention, chemotherapy (and its emetogenicity) protocol, control intervention, and patient population. However, results were positive in five out of the six trials. Hypnosis was effective for both anticipatory and post-treatment nausea and vomiting, although results were not reported separately for acute and delayed nausea and vomiting. A large effect for hypnosis was found when compared with usual care. A moderate effect for hypnosis was found when compared with therapist contact, and a small effect for hypnosis when compared with cognitive-behavior therapy.

Other forms of mind–body therapies have also been evaluated for chemotherapy-induced nausea and vomiting [46–48]. The interventions in these studies were mainly progressive muscle relaxation (PMR), and guided imagery. PMR is a technique for reducing anxiety by alternately tensing and relaxing the muscles. Guided imagery refers to the use of imagination to invoke one or more of the senses, thereby guiding an individual through sensory experiences to promote physical and emotional wellbeing. Although the studies were heterogeneous in terms of patient population and treatment style, patients benefited in both the control of nausea and vomiting (for anticipatory, acute and delayed nausea and vomiting) and improvement in quality of life. Although it is inconclusive whether or not such treatments are effective, their excellent safety profile and potential for empowering patients make them noteworthy in supportive care. Thus, the British National Institute for Clinical Excellence consultation guidelines for improving outcomes in children and young people with cancer recommend that “there should be timely access to occupational and psychological or behavioral therapies for patients with anticipatory nausea and vomiting [49].

Yoga is a traditional Indian practice that includes several techniques, such as asanas (postures done with awareness), pranayama (voluntarily regulated nostril breathing), yoga nidra (guided relaxation with imagery) and meditation, which aim to promote physical well-being and mental calmness. Yoga is thought to modulate the perceptions and mental responses to both external and internal stimuli. Raghavendra et al. randomized 62 subjects to either yoga (n = 28) or a control group (n = 34) [50]. Yoga intervention significantly helped to reduce the frequency and intensity of post-chemotherapy nausea by 18%, and anticipatory nausea by 12% and 18%, and vomiting intensity by 9% as compared with controls. These findings indicate that the beneficial effects observed in this study can be attributed to yoga practices that help in stress reduction, rather than to mere social support and education.

**Summary**

Mucositis, xerostomia, nausea and vomiting continue to inflict substantial morbidity and impaired quality of life among people undergoing chemotherapy and/or radiotherapy. In this article we reported CAM therapies with potential effectiveness in reducing these side effects. Balancing the safety and efficacy
of these therapies, we recommend that primary care providers and oncologists inform their patients of their potential for complementing standard of care. Guidelines in supportive care should include recommendations for appropriate CAM therapies for these conditions. Further research should be strongly encouraged in order to uphold the value of medical pluralism, and be able to better inform patients and their physicians.

Conflict of interest

No conflict of interest declared.

References


