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REVIEW ARTICLE

A systematic review of dysgeusia induced by cancer therapies

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Abstract
Purpose The purpose was to review relevant scientific papers written since 1989 which focused on the prevalence and management of dysgeusia as an oral side effect of cancer treatment.
Methods Our literature search was limited to English language papers published between 1990 and 2008. A total of 30 papers were reviewed; the results of 26 of these papers were included in the present systematic review. A structured assessment form was used by two reviewers for each paper. Studies were weighted as to the quality of the study design, and treatment recommendations were based on the relative strength of each paper.
Results A wide range in reported prevalence of dysgeusia was identified with the weighted prevalence from 56–76%, depending on the type of cancer treatment. Attempts to prevent dysgeusia through the prophylactic use of zinc sulfate or amifostine have been of limited benefit. Nutritional counseling may be helpful to some patients in minimizing the symptoms of dysgeusia.

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Conclusions Dysgeusia is a common oral side effect of cancer therapy (radiotherapy, chemotherapy, or combined modality therapy) and often impacts negatively on quality of life. From the current literature, there does not appear to be a predictable way of preventing or treating dysgeusia.

Keywords Dysgeusia · Cancer therapy · Amifostine

Introduction

Dysgeusia is variably defined as an abnormal or impaired sense of taste, an unpleasant alteration of taste sensation, or a distortion or perversion of the sense of taste. Dysgeusia can be described as a bitter, metallic, salty, or unpleasant taste. Dysgeusia is closely linked to changes in olfaction as both taste and smell are involved in producing the sense of flavor. Taste and olfaction provide sensory information and sensory pleasure and it is known that cancer therapies affect both [14].

Alterations in taste and smell in cancer patients, due to either malignancy itself or therapeutic interventions, is a prevalent problem. These alterations affect the daily quality of life of these patients and may lead to patient malnutrition, weight loss and, in severe cases, significant morbidity [13, 30].

Dysgeusia is assessed clinically by measuring the detection or recognition threshold values for the five basic tastes: sweetness, bitterness, sourness, saltiness, and umami (the savoriness of protein-rich foods), either by applying filter-paper taste strips impregnated with various concentrations of a basic taste or, in the laboratory setting, with the use of an instrument called an electrogustometer. However, these methods do not provide qualitative information on taste acuity such as which basic taste perception is most influenced by cancer or its treatment. Qualitative changes are, instead, reported through patient complaints, interviews, and clinical observations [15].

The exact mechanism underlying the observed taste and odor disturbances in cancer patients is not yet known for several reasons. First, studies of taste and odor problems have been investigated in heterogeneous cancer patient populations with wide variations in the type of complaints and their severity. These large variations in symptoms among these patients make it difficult to correlate sensory disturbances with specific biologic markers. Second, metabolism in cancer patients is orchestrated by numerous exogenous and endogenous factors that interact with one another in complicated ways. Thus, it is difficult to screen for a certain factor responsible for taste and odor abnormalities among these interconnected factors. There is agreement, however, that damage to sensory receptor cells and abnormal neuronal activities are independent causes of the taste and odor abnormalities in these patients, but the etiology of these disorders is likely multifactorial.

Chemotherapy and radiotherapy may cause taste and odor disturbances by destroying taste and olfactory receptor cells. Cell damage may occur in three ways: (1) a decrease in the number of normal receptor cells, (2) alteration of cell structure or receptor surface changes, and (3) interruption in neural coding. The turnover rate of normal human taste bud cells is 10 days, and the lifespan of olfactory receptor cells is about 1 week. Radiation therapy and cytotoxic chemotherapeutic agents kill cells with high turnover rates.

Radiation therapy may lead to dysgeusia by altering the structure of taste pores (resulting in disrupted delivery of flavor molecules to receptor cells) or by causing a thinning of the papilla epithelium.

Cancer treatment may also affect neuronal activities as well as receptor cells. Abnormal sensitization of the chorda tympani nerve can result in specific taste sensations without stimulating the taste receptors or requiring the presence of the corresponding flavor molecules. Anti-neoplastic drugs may damage neuronal cells, thus modifying afferent taste pathways.

Recent research has indicated that lipid peroxidation of oral epithelial cells may contribute to the production of carbonyls that cause a metallic taste sensation. Ferrous iron reacts with human skin and produces a series of aldehydes and ketones causing a metallic odor. A similar mechanism likely produces the metallic flavor in the mouth.

Bitter and metallic sensations may also originate from the taste of chemotherapeutic drugs. Many of these drugs have bitter-tasting compounds that can enter the mouth through crevicular fluid from plasma or may diffuse from capillaries to the posterior of taste or odor receptor cells. Drugs other than anti-neoplastic agents, including antibiotics and analgesics (which are often taken by cancer patients to manage side effects) are also able to influence taste perception.

Other possible causes of unpleasant taste alterations that cancer patients experience may be the extraneous substances produced by poor oral hygiene, infection, postnasal drip, gastrointestinal reflux, and oral mucositis [15].

Finally, both chemotherapy and radiotherapy can alter the pleasure produced by taste and smell through the formation of conditioned aversions. That is, foods consumed in proximity with the nausea of therapy come to be unpleasant. The 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies and the publication of the National Cancer Institute Monographs in 1990 offered some clinical recommendations to minimize the formation of conditioned aversions [1].

Since 1989, there have been significant advances in cancer therapies, particularly in the treatment of head and

neck cancers. Chemotherapy is much more commonly used (in combination with radiotherapy) in the management of head and neck cancers. The introduction of Intensity-Modulated Radiation Therapy and other three-dimensional radiotherapy techniques have allowed an escalation of effective dose to the tumor site while offering the potential to limit radiation dose to vital structures outside of the tumor bed.

The aim of this systematic review, therefore, was to provide a follow-up on the 1989 NIH document and to specifically look at the following issues:

- To determine the reported prevalence of dysgeusia by cancer therapy regimen
- To determine the impact of dysgeusia on quality of life
- To comment on the economic impact of dysgeusia
- To assess management strategies for dysgeusia

Methodology

A research librarian performed literature searches using the following online databases: Medline/PubMed, EMBASE, and Cochrane Library. The period searched was between 1990 and 2008. The search focused on studies reporting dysgeusia as a side effect of cancer therapy. Although the majority of the papers involved patients with various head and neck cancers, there were also papers which looked at patients being treated for hematologic malignancies and other cancers (breast, lung, prostate, etc). Searches were limited to studies involving human subjects that were published in the English language journals. The publication types included in this review were: randomized (RCT) and non-randomized clinical trials (N-RCT), cohort studies, before and after studies, and case–control studies.

The review of literature and development of recommendations were based on the manual provided by leaders of the Oral Care Study Group (OCSG) of the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology. This manual was created as part of the larger Oral Care Systematic Review project of which dysgeusia was one of the ten sections being reviewed. As part of the preparation for the systematic review, the methodology proposed by the leaders of the OCSG was tested by the sections' heads. An identical form was completed by all members of the systematic review to test for calibration. Each of the studies was independently reviewed by two members of the dysgeusia section. Each of the reviewers discussed their review results and concluded their final decision in any areas of disagreement.

Dysgeusia was assessed by the presence (Y/N) or grade when available. Measures of quality of life (QOL) and economic variables were documented if available. The quality of selected articles was assessed and scored with respect to sources of bias, representativeness, scale validity, and sample size. These parameters were utilized to determine the weighted prevalence of dysgeusia. Further details of this methodology can be reviewed elsewhere in this monograph [36].

Results

Thirty articles were reviewed as part of the literature search. Three of the articles were excluded because the paper did not report dysgeusia findings [3, 10, 25], and a fourth article was excluded because the study did not involve cancer patients or cancer therapy [14]. The remaining 26 papers were classified according to their study design: studies were identified as randomized clinical trials (5), non-randomized clinical trials (1), cohort studies (13), before and after studies (6), or case–control studies (1). Fourteen studies evaluated patients treated for squamous cell carcinoma, nine evaluated patients treated for solid tumors, and three assessed a wide range of cancer diagnoses.

Of the 26 studies evaluated, only fourteen of the studies (54%) used a standard, validated scale in the assessment of dysguesia; in seven of the studies (27%), a study-specific dysgeusia scale was used.

Prevalence

The prevalence of dysgeusia could be determined from 14 studies where the presence of dysgeusia was appropriately assessed using a standardized, validated scale. The weighted prevalence for dysgeusia in the chemotherapy only group was 56.3%, the radiotherapy only group was 66.5%, and the combined RT and CT was 76% (Table 1). Approximately, 15% of patients treated with RT continued to experience dysgeusia after the completion of treatment.

Observational studies

Among the 13 cohort studies and one case–control study, the frequency and severity of dysgeusia is presented relative to the cancer therapy involved.

Head and neck radiotherapy

Five studies looked at patients receiving high-dose radiotherapy for treatment of various head and neck

Table 1 Weighted prevalence of dysgeusia during cancer therapy

	Number of studies (reference)	Mean prevalence (%)	Standard error	95% Confidence interval
During cancer therapy				
Chemotherapy only	5 (von Poznak, Macquat-Moulin, Maisono, Beale, Ohrn)	56.3	0.15	15.0–97.6
Radiotherapy only	5 (Lu, Winter, Kearvall, Hughes, Amosson)	66.5	0.14	26.8–100.0
Radiotherapy and chemotherapy	3 (Fang, Just, Denis)	76.0	0.24	0.0–100.0
After cancer therapy				
Radiotherapy	2 (Lu, Hainsworth)	14.9	0.05	0.0–80.0

cancers. The studies varied in design, and the reported frequency of dysgeusia ranged from 32% to 100%. In one study, dysgeusia complaints seemed proportional to the RT dose to the parotid gland [2]. In another study which followed patients over time, the frequency of dysgeusia as a complaint decreased over time [22]. In all studies, the severity of dysgeusia was rated as mild [2, 8, 17, 22, 34]. In four before and after (i.e., quasi-experimental, non-controlled, non-randomized) studies involving RT alone, the rate of dysgeusia ranged from 16–100% [7, 8, 19, 22] and was usually reported as mild to moderate in severity.

During a course of curative head and neck radiotherapy (60–70 Gy/6–8 weeks), taste dysfunction becomes measurably impaired during the first week of treatment and becomes worse during the second week. The greatest degree of compromise is reached during the third or fourth week of treatment. A dose of 60 Gy causes a relative taste loss in over 90% of patients and tends to last throughout the entire course of radiotherapy. Taste loss is generally not observed until radiation doses of 20 Gy have been administered in the head and neck regions. A partial improvement in taste can usually be found between the 20th to the 60th day after termination of radiotherapy and taste generally returns to normal or near-normal levels within 1 year after radiotherapy. However, in some patients, taste changes may persist up to 7 years following radiotherapy [28].

Irradiated iodine therapy

In the one study that assessed patients treated with irradiated iodine for various forms of thyroid cancer, only 9/71 (9.8%) of patients reported dysgeusia symptoms [29].

Combined modality therapy (RT +/− CT)

In a study that evaluated 44 patients who either received radiotherapy or radiochemotherapy for various head and neck cancers, the rate of dysgeusia was found to be higher (41% vs. 30%) in patients receiving radiotherapy alone (7/17 patients) compared to patients receiving combined modality therapy (8/27 patients) [6].

In contrast, another study found that combined modality therapy produced more severe symptoms of dysgeusia although all 37 patients in this study experienced some degree of dysgeusia, regardless of whether chemotherapy was involved or not [16].

A third study, evaluating 38 head and neck cancer patients treated with radiotherapy +/− chemotherapy, reported that all patients had some degree of dysgeusia although the grade of dysgeusia was never reported as severe [32].

Ohrn et al. reported that dysgeusia scores were generally higher among radiotherapy patients than in chemotherapy patients and that the severity of dysgeusia was most directly related to the cumulative RT dose [26].

One case−control study was reviewed, in which 12 head and neck cancer patients, all having received combined modality treatment and all reporting dysgeusia post-treatment, were compared with 12 control patients in terms of ultra-structural tongue changes (as visualized by confocal microscopy). The results indicated that epithelial changes in the fungiform papilla (but not in the taste bud structure) were predictive of dysgeusia [18].

In before and after studies involving combined modality therapy, the incidence of patient-reported dysgeusia was generally lower, ranging from 10–44% [8, 11, 31] and, again, was generally reported as mild in nature.

Chemotherapy

Three studies looked at the effects of chemotherapy used as mono-therapy for various cancers: the first study reviewed 42 patients with various solid organ tumors enrolled in a phase I study; the second study reviewed 95 patients with inflammatory breast cancer patients; a third study reviewed 30 patients with metastatic breast cancer [4, 23, 24].

Dysgeusia was reported in 16.6%, 67%, and 100% of the patients, respectively, and was always reported as mild–moderate in severity. In the one study that followed patients over time, dysgeusia returned to baseline levels 1 year following the cessation of therapy [23].

Impact on quality of life

Fourteen of the studies reviewed reported specifically on the impact of dysgeusia on patient-reported quality of life, using either a validated quality-of-life questionnaire, a visual analogue scale or a study-specific quality-of-life scale [2, 7–9, 12, 16, 18–20, 23, 27, 33]. The results were variable and difficult to interpret as dysgeusia was often reported along with a number of other quality-of-life measures (xerostomia, oral pain, swallowing, social eating, etc). Nonetheless, some general comments can be made pertaining to dysgeusia as it relates to patient-reported quality of life:

- Oropharyngeal complaints (including dysgeusia) are common and significant in patients undergoing head and neck cancer therapy and can result in profound decreases in quality of life.
- Some head and neck patients experience a deterioration in quality of life (QOL) following head and neck radiotherapy relative to taste changes; more commonly, there are other QOL measures that are more significant sources of distress to head and neck patients (dry mouth, sticky saliva, difficulty swallowing, and oral pain).
- Dysgeusia becomes more problematic as radiotherapy dose increases but often disappears as an oral complaint following the cessation of therapy.

Economic impact

There were no studies evaluating the economic impact of dysgeusia.

Prevention and/or management strategies

Zinc supplementation

The specific role of zinc in relation to taste perception is unknown, but it is a recognized cofactor of alkaline phosphatase, which is the most abundant enzyme within the taste bud membrane. In addition, zinc may play a role in the conformation of proteins involved in regulation of the pores of taste bud microvilli [26, 28].

Studies that specifically examined prevention and/or management strategies for dysgeusia using zinc provided variable results. One study examined the use of zinc gluconate in the management of idiopathic dysgeusia in a non-cancer population and found that zinc appears to improve general gustatory function and, consequently, general mood scores in dysgeusia patients [13]. Another study evaluated 169 patients receiving RT +/− chemotherapy for head and neck cancers; 84/169 were randomized to receive 45 mg zinc sulfate orally tid starting on the first day of RT and continuing for 1 month after the completion of RT, the second group (85/169) received a placebo. The results showed no statistically significant difference between the two groups in terms of dysgeusia (73% in the zinc-treated group; 84% in the placebo-treated group) [12].

Amifostine

Cytoprotective agents such as amifostine have been studied relative to the prevention and/or management of dysgeusia. Amifostine is a thiol compound which protects normal organs and tissues from oxidative damages induced by cancer therapy by the scavenging of free radicals produced by either chemotherapy or radiotherapy [15].

The two studies that looked at the use of amifostine in preventing dysgeusia showed that while amifostine reduced the incidence and severity of acute and late toxicities in general, the effects of amifostine on dysgeusia specifically were not as impressive. In one study, both arms of the study (amifostine-treated and control patients) experienced dysgeusia at the same rate [5]; the second study (examining the effects on amifostine on acute toxicity of concurrent chemotherapy and radiotherapy on lung patients) showed that dysgeusia was more frequent among patients given amifostine than among controls (32% vs. 10%; $p=0.039$) [21].

Dietary and educational counseling

Two RCTs investigated the use of dietary counseling and educational tapes on the incidence and severity of oral side effects of cancer therapy, including dysgeusia. The first study showed that dietary counseling had a minor impact on early-onset dysgeusia (30% vs. 40%) but a more significant effect on long-term dysgeusia as an oral side effect (5% vs. 25%) [27]. The second study showed that the use of audiotapes as an educational tool for patients was no more effective than simply mailing patients written information in lessening the early and late reporting of dysgeusia as an oral side effect of cancer therapy. In both groups, the rate of dysgeusia ranged from 54% to 68% [33].

Overall, the results of RCTs are discouraging: amifostine seems only modestly helpful in reducing the severity (not the incidence) of dysgeusia; zinc sulfate does not seem any better than placebo; dietary

counseling is of modest benefit to some patients, but the manner in which patient education is delivered does not seem to make a difference.

RT decrease to the tip of tongue

One N-RCT was reviewed which looked at 118 patients with head and neck cancer treated with RT +/− chemotherapy. One group had the tip of the tongue in the RT field; the second group did not. The results reported no patients' complaints of dysgeusia when the tongue tip was not in the RT field; by contrast, for patients who had the tip of the tongue included in the RT field, there were marked increases in mean threshold values to the four taste qualities being tested (salt, sweet, sour, and bitter) [35].

Conclusions of the review

- From the few studies that have reported the prevalence of dysgeusia, approximately half of patients being treated with CT alone experienced dysgeusia, while two thirds of patients treated with RT and three fourths of patients treated with combined RT and CT experienced dysgeusia.
- Approximately 15% of patients treated with RT continue to experience dysgeusia after the completion of treatment.
- Dysgeusia does have an impact on QOL, but future studies need to further clarify our understanding of this relationship.
- A long-term, multicenter prospective study of patients treated with newer treatment modalities for various cancers is needed to determine the prevalence, QOL, and economic impact of this common oral complication.
- Our systematic review failed to demonstrate any significant improvement of dysgeusia from various treatment strategies.
- Newer preventive and management strategies are needed.

Prevention strategies (with level of evidence, recommendation grade and guideline classification)

Zinc gluconate

Level of evidence II, recommendation grade C, suggestion to not use zinc gluconate to prevent dysgeusia in head and neck cancer patients, although this has been found to be beneficial in a non-cancer idiopathic dysgeusia cohort.

Amifostine

Level of evidence II, recommendation grade B, recommend not to use amifostine solely for the prevention of dysgeusia in head and neck cancer patients.

Dietary and educational counseling

Level of evidence II, recommendation grade B, suggestions to use counseling for the prevention of dysgeusia

Recommendations for future research directions

There is a clear need for the development and use of validated tools for the clinical evaluation of dysguesia in the research setting. Considering the high prevalence of dysgeusia in published studies and the QOL deficits associated with dysgeusia, increased efforts for patient education and prevention and early treatment options are warranted. Larger prospective trials for the prevention and treatment of dysgeusia are needed to improve management of this oral sequela often seen during cancer therapy.

Conflict of interest statement None declared.

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