Int. J. Radiation Oncology Biol. Phys., Vol. 67, No. 5, pp. 1318–1322, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.10.046

CLINICAL INVESTIGATION **Head and Neck**

DOES ZINC SULFATE PREVENT THERAPY-INDUCED TASTE ALTERATIONS IN HEAD AND NECK CANCER PATIENTS? RESULTS OF PHASE III DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL FROM THE NORTH CENTRAL CANCER TREATMENT GROUP (N01C4)

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Purpose: **Taste alterations (dysgeusia) are well described in head and neck cancer patients who undergo radiotherapy (RT). Anecdotal observations and pilot studies have suggested zinc may mitigate these symptoms. This multi-institutional, double-blind, placebo-controlled trial was conducted to provide definitive evidence of this mineral's palliative efficacy.**

Methods and Materials: **A total of 169 evaluable patients were randomly assigned to zinc sulfate 45 mg orally three times daily vs. placebo. Treatment was to be given throughout RT and for 1 month after. All patients were scheduled to receive ≥2,000 cGy of external beam RT to ≥30% of the oral cavity, were able to take oral medication, and had no oral thrush at study entry. Changes in taste were assessed using the previously validated Wickham questionnaire.**

Results: **At baseline, the groups were comparable in age, gender, and planned radiation dose (<6,000 vs. ≥6,000 cGy). Overall, 61 zinc-treated (73%) and 71 placebo-exposed (84%) patients described taste alterations during the first 2 months ($p = 0.16$). The median interval to taste alterations was 2.3 vs. 1.6 weeks in the zinc-treated and placebo-exposed patients, respectively ($p = 0.09$). The reported taste alterations included the absence of any taste (16%), bitter taste (8%), salty taste (5%), sour taste (4%), sweet taste (5%), and the presence of a metallic taste (10%), as well as other descriptions provided by a write in response (81%). Zinc sulfate did not favorably affect the interval to taste recovery.**

Conclusion: **Zinc sulfate, as prescribed in this trial, did not prevent taste alterations in cancer patients who were undergoing RT to the oral pharynx.** **© 2007 Elsevier Inc.**

Zinc sulfate, Taste alterations, Head-and-neck cancer, Phase III trial.

INTRODUCTION

Radiotherapy (RT) to the oral cavity can cause taste alterations. Patients have described an overall decreased sense of taste or a distortion of normal taste. These changes carry notable implications (1). First, although data are scant, it has been assumed that taste alterations negatively affect a patient's overall quality of life. MacCarthy-Leventhal (2), a physician who had been diagnosed with head and neck cancer and herself underwent RT to the oral cavity, described these quality-of-life effects as follows:

> It is difficult to explain to other people this "blindness of the mouth." They can bandage their eyes, but they find it hard to imagine the disgust and suspicion engendered by a "cindery bolus" in the blind mouth. Those faithful sentries, the taste buds, are dead.

MacCarthy-Leventhal died of cancer in 1959, and her personal case report was published posthumously. It provides a revealing account of the taste alterations from the patient's perspective. Second, taste alterations can predispose to malnutrition, which may in turn lead to negative clinical outcomes, such as greater rates of adverse events from RT, cancer treatment delays, and compromised tumor control. Colasanto *et al.* (3) recently reviewed the implications of nutritional compromise in head and neck cancer patients undergoing RT. These authors underscored the

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This study was conducted as a collaborative trial of the North Central Cancer Treatment Group and Mayo Clinic and was supported in part by Public Health Service Grants CA-25224, CA-37404, CA-60276, CA-35119, CA-63849, CA-35113, CA-35431, and CA-63848.

Conflict of interest: none.

Received Sept 15, 2006, and in revised form Oct 25, 2006. Accepted for publication Oct 30, 2006.

importance of addressing factors that may predispose to malnutrition, such as taste alterations.

Recognizing the need to address this issue, Ripamonti *et al.* (4) conducted a placebo-controlled pilot study to test the role of zinc in head and neck cancer patients undergoing RT. The second most abundant trace mineral in the human body, zinc was chosen as a palliative intervention because it plays a critical role in wound repair and maintenance of immunity and because anecdotal reports had suggested it might reverse taste alterations in noncancer settings (5–7). Thus, Ripamonti *et al.* (4) treated 18 patients with zinc 45 mg orally 3 times daily vs. placebo at the first sign of taste alterations. Taste acuity was determined by measuring the detection and recognition thresholds for four taste qualities: sweet, sour, bitter, and salty. The placebo-exposed patients manifested worsening of taste acuity for all four qualities compared with the zinc-treated patients. One month after RT, the patients who had received the zinc sulfate had recovered their taste more quickly. These provocative pilot data suggested that zinc sulfate merited further study in cancer patients.

The North Central Cancer Treatment Group (NCCTG) therefore embarked on a multi-institutional, placebo-controlled trial to test the role of zinc sulfate in head and neck cancer patients at risk of taste alterations as a result of cancer therapy and also at risk of the potential decline in quality of life and compromise of clinical outcomes associated with dysgeusia.

METHODS AND MATERIALS

Overview

This Phase III trial was conducted within the NCCTG. The institutional review boards at each specific study site within the NCCTG approved the study protocol before the patients were enrolled. All patients provided written informed consent before participation in the trial.

Patient eligibility

Head and neck cancer patients scheduled to receive ≥2,000 cGy of external beam RT to ≥30% of the oral cavity were eligible for the study. All had to be ≥18 years of age, with a life expectancy of ≥3 months, as determined by the physician's judgment. All were required to have an Eastern Cooperative performance score of 0, 1, or 2. At enrollment, the patients had to be able to take oral medications reliably and to be alert and competent. Patients receiving amifostine and/or concomitant chemotherapy were allowed to participate in the trial.

Patients were ineligible if they had any one of the following: known mechanical obstruction of the alimentary tract, malabsorption, or intractable vomiting; previous surgery that had included ablation or removal of the olfactory component of taste; known intolerance to zinc sulfate; or untreated oral thrush. In addition, women who were pregnant, nursing, or of childbearing potential and unwilling to use contraception were excluded.

Pretreatment and follow-up evaluations

All patients underwent history, physical examination, and determination of performance status within 7 days of trial registration. Monitoring included assessment of parameters to evaluate the efficacy of zinc sulfate vs. placebo. These assessments occurred weekly during RT and at 1, 2, 3, and 6 months after RT completion. Various parameters were used to evaluate the efficacy of zinc sulfate vs. placebo. The assessment parameters included patient-reported taste alterations, using a previously validated questionnaire from Wickham *et al.* (8); a general quality-of-life questionnaire that used a linear analog assessment scale (9); and physician-reported patient weight. In addition, the study tracked patients who required cessation of RT because of radiation-induced toxicity within each treatment group. Adverse event data that were physician reported were graded using the Common Toxicity Criteria, version 2.

Treatment

Before randomization, patients were stratified according to the following parameters: *(1)* planned radiation dose (<6,000 vs. ≥6,000 cGy); *(2)* estimated amount of oral cavity mucosa in the radiation field (>60% vs. ≤60%); *(3)* patient age (<50 vs. ≥50 years); and *(4)* concomitant chemotherapy planned (yes vs. no). Next, the patients were randomly assigned to receive zinc sulfate 45 mg orally 3 times daily after meals vs. an identical-appearing placebo prescribed at the same frequency. The zinc sulfate/placebo was to start within 7 days of the initiation of RT and was to continue for another 4 weeks after RT completion. The selection of the dose was determined by comparability with that tested by Ripamonti *et al.* (4).

Dose reductions of the study agents were to occur in the event of gastrointestinal intolerance, which was to trigger a decrease in the dose to twice daily, along with a recommendation to take the agent with food. The protocol called for discontinuation of therapy in the event of intolerable bloating or stomach upset. Other adverse events attributable to the study drug were to be handled according to the discretion of the treating oncologist.

Statistical Analysis

The primary objective of this trial was to determine whether zinc sulfate delayed the onset of taste alterations in head and neck cancer patients undergoing RT. The primary endpoint was measured with select questions from the Wickham questionnaire. Patient responses were transformed to a 100-point system, with 0 indicating severe taste alteration and 100, no taste alteration. A 10% decline in score from baseline at any point indicated evidence of taste alteration. The interval to the first taste alteration was used to measure the primary endpoint. Taste preservation curves were constructed using the Kaplan-Meier method, and a log–rank test was used to determine differences between groups. Patients who required cessation of RT or treatment interruptions were censored. Analogously, the interval to taste recovery was also explored. Various factors, such as baseline or anticipated use of nutritional support denture use, smoking status, and the use of amifostine were introduced into the analyses to further explore the differences between groups using a Cox proportional hazards model.

A 10% decline in taste as detected by the Wickham questionnaire would represent a one-half standard deviation drop, or a moderate effect size. Patients who manifested such a decline were to be deemed to have prophylactic failure. A total of 84 patients per group (168 total) provided 90% power to detect this difference with a two-sided test, with a 5% type I error rate. With a median interval to taste alteration of 2 weeks after the initiation of RT, this

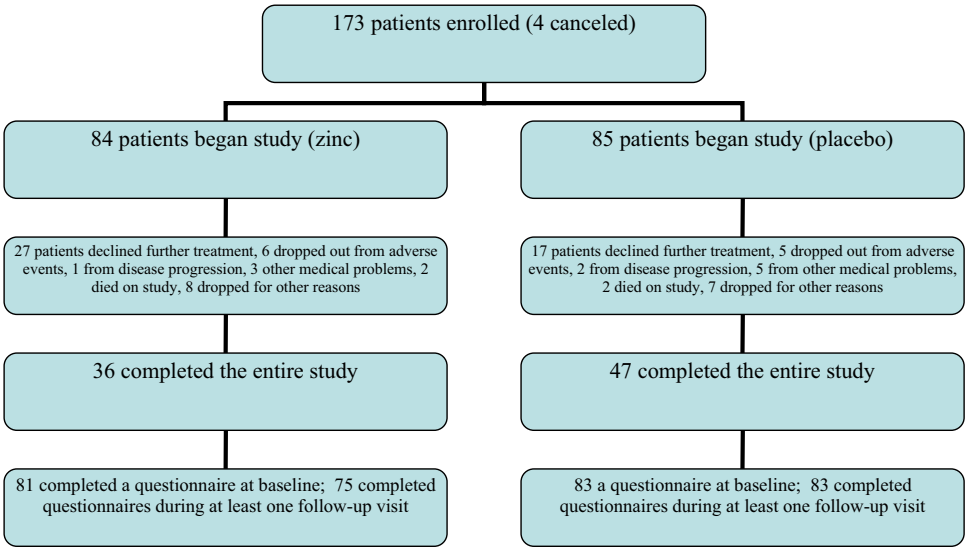

Fig. 1. Consort diagram.

sample size enabled the study team to discern a prolgation of taste preservation from 2 to 3.5 weeks with 90% power.

The secondary endpoints included the incidence of taste alteration, patient-reported quality of life, adverse events, and weight loss. The taste alteration incidence was compared between the two treatment arms using Fisher's exact test for both patient-reported and physician-reported taste changes. These differences were assessed 2 months after treatment. The linear analog self-assessment scales were transformed to a 0–100 scale for comparability, and *t* tests were performed to determine differences in mean scores between the arms. Adverse events were summarized in a descriptive fashion. In addition, patients were categorized on the basis of whether they had lost ≥5% of their pretreatment weight at the 2-month reevaluation point. The incidence of weight loss and premature RT cessation were compared between groups using Fisher's exact test. In an exploratory fashion, analyses were done with *t* tests to assess whether the development of taste alterations were associated with the global quality-of-life scores.

RESULTS

Between May 2002 and October 2005, 173 patients were randomized to a study arm. Subsequently, 4 received no study treatment, leaving 169 evaluable patients (Fig. 1). The patient baseline characteristics are listed in Table 1. The median patient age was 59 years (range, 31–88 years). Of the 169 patients, 70% were men. The two treatment groups were well balanced with respect to all the baseline features, including the anticipated use of amifostine and implementation of nutrition support at baseline.

Compliance throughout the study was favorable. Overall, most patients reported almost always taking the proper amount of study agent on a weekly or monthly basis. More than 70% of patients described near-perfect compliance during the first month.

Overall, 61 zinc-treated (73%) and 71 placebo-exposed (84%) patients described taste alterations during the first 2 months ($p = 0.16$). Patients described an absence of any taste (16%), bitter taste (8%), salty taste (5%), sour taste (4%), sweet taste (5%), and the presence of a metallic taste (10%). Additionally, 81% of patients provided additional write-in details on the foregoing taste alterations, as well as further information on other aspects of taste alterations. Many of these comments described how the tongue felt "burned" or how food had acquired a "pepper" taste, a "greasy" taste, a "soapy" taste, a "powdery" taste, or a "chemical" taste. One person described how food tasted, "just plain awful." Another patient commented on how dairy products remained the most appealing.

With regard to the primary endpoint, no statistically significant differences were found in the interval to taste alter-

Table 1. Baseline characteristics*

Characteristic	Zinc ($n = 84$)	Placebo ($n = 85$)	p
Age (y)			0.99
Median	59	58	
Range	31–88	38–95	
Gender *(n)*			0.83
Female	26 (31)	25 (29)	
Male	58 (69)	60 (71)	
Planned radiation dose (cGy)			
<6,000	16 (19)	15 (18)	0.81
≥6,000	68 (81)	70 (82)	
Anticipated oral cavity in radiation field (%)			
≤60	41 (49)	36 (42)	0.40
>60	43 (51)	49 (58)	
Concomitant chemotherapy anticipated *(n)*	37 (44)	34 (40)	0.59
Amifostine anticipated *(n)*	21(25)	21 (25)	0.96
Smoker *(n)*	15 (18)	13 (15)	0.65
Dentures present *(n)*	25 (30)	26 (31)	0.90
Nutritional support started at baseline *(n)*	4 (5)	5 (6)	0.75

*Data in parentheses are percentages.

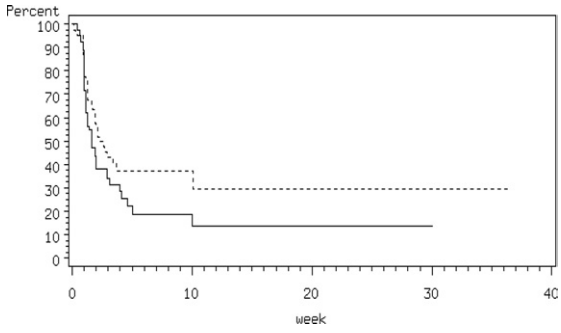

Fig. 2. Median interval to patient-reported alterations in taste for zinc-treated (dotted line) and placebo-exposed (solid line) patients ($p = 0.09$).

ations between the two groups. The median interval to patient-reported alterations in taste was 2.3 weeks vs. 1.6 weeks in zinc-treated and placebo-exposed patients, respectively ($p = 0.09$; Fig. 2). The Cox regression model analysis for the interval to taste alteration showed that the only factor that had a significant affect in influencing the outcome was the amount of oral mucosa in the radiation field ($p = 0.004$). The planned radiation dose, patient age, planned concomitant chemotherapy, smoking status, denture use, baseline institution of nutrition support, and administration of amifostine did not reveal any differences in the interval to taste alterations between the two groups.

Zinc sulfate did not favorably affect most other clinical parameters either. No difference was found in the number of the interruptions in RT according to treatment arm. Nor did zinc sulfate favorably affect the interval to taste recovery. Throughout the whole study period, 4 zinc-treated patients reported taste recovery in contrast to 13 placebo-exposed patients.

The baseline overall quality-of-life scores were favorable (median score 80, with 100 the best quality-of-life score imaginable). Over time, no statistically significant differences were found in the scores when stratified by treatment arm (Fig. 3). Curiously, correlations between the overall quality-of-life scores and the presence of taste alterations were weak, between 0.1 and 0.2 over time.

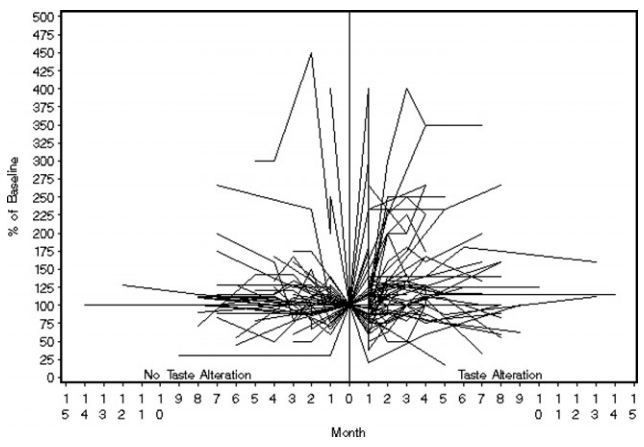

Fig. 3. Symmetry in change of quality of life from baseline with no major differences when stratified by presence of taste alterations.

Table 2. Select severe adverse events

Adverse event	Zinc ($n = 76$)	Placebo ($n = 83$)	p*
Anorexia			0.90
Grade 3	2 (3)	2 (2)	
Grade 4	2 (3)	1 (1)	
Arrhythmia (Grade 3)	1 (1)	0 (0)	0.30
Ataxia (Grade 3)	1 (1)	0 (0)	0.30
Constipation (Grade 3)	2 (3)	1 (1)	0.79
Dehydration (Grade 3)	4 (5)	2 (2)	0.35
Dermatitis			0.83
Grade 3	0 (0)	2 (2)	
Grade 4	1 (1)	0 (0)	
Dysphagia (Grade 3)	3 (4)	0 (0)	0.02
Dyspnea (Grade 3)	1 (1)	1 (1)	0.95
Fatigue (Grade 3)	1 (1)	0 (0)	0.30
Gastrointestinal (Grade 3)	1 (1)	0 (0)	0.30
Headache (Grade 3)	1 (1)	0 (0)	0.30
Hypoxia (Grade 3)	2 (3)	0 (0)	0.14
Infection, not wound related			0.34
Grade 3	2 (2)	1 (1)	
Grade 4	0 (0)	1 (1)	
Mucositis			0.42
Grade 3	16 (21)	16 (19)	
Grade 4	3 (4)	2 (2)	
Nausea (Grade 3)	4 (5)	5 (6)	0.39
Neurologic (Grade 3)	1 (1)	0 (0)	0.30
Neutropenia			0.18
Grade 3	0 (0)	1 (1)	
Grade 4	0 (0)	1 (1)	
Stomatitis (Grade 3)	1 (1)	2 (2)	0.27
Thrombosis (Grade 4)	1 (1)	0 (0)	0.30
Vomiting (Grade 3)	2 (3)	3 (4)	0.84
Wound infections (Grade 3)	0 (0)	1 (1)	0.34

Data presented as numbers, with percentages in parentheses.
* Although only severe adverse events shown, p values were based on analyses of adverse events of all severity levels.

In terms of physician-reported weight data, as many as 99% of zinc-treated patients maintained their weight in contrast to 92% of placebo-exposed patients ($p = 0.04$).

Finally, zinc sulfate was well tolerated. A greater percentage of zinc-treated patients described moderate or severe dysphagia compared with placebo-exposed patients: 7% vs. 4%, respectively ($p = 0.02$). Otherwise, adverse events were relatively rare with comparable frequencies and severity between two study arms (Table 2).

DISCUSSION

To our knowledge, this study is the largest ever reported to date to evaluate zinc sulfate in the treatment or prevention of taste alterations. The results are disappointing. Zinc sulfate did not significantly increase the interval to taste alterations, nor did it appear to decrease the incidence of taste alterations or the interval to taste recovery. It is impossible to know how often zinc is prescribed to cancer patients for this indication, but the negative findings from this study

indicate that zinc sulfate, as administered in this trial, should not be prescribed to cancer patients under these circumstances and for this purpose.

Why might the results of this study differ from those of the study by Ripamonti *et al.* (4)? There were two major differences in study design between our trial and the trial reported by Ripamonti *et al.* (4). First, their study tested the recognition thresholds to measure taste acuity. In contrast, our study used a validated, patient-completed questionnaire. The former is not practical in the setting of a multi-institutional study. Moreover, the reliance on patients' reported assessment of taste, based on foods eaten on a daily basis, does constitute a clinically meaningful endpoint. Thus, although one might invoke differences in the measurement of the primary study endpoint, one could argue that both methods are valid, capable of generating meaningful data, and unlikely to explain the divergent conclusions from these two studies. Second, and more importantly, the present study was almost 10-fold larger and was designed to provide definitive conclusions on the role of zinc in preventing therapy-induced taste alterations. The robust nature of the NCCTG study reported here likely accounts for the contrastingly negative conclusions on zinc sulfate in preventing dysgeusia.

It is important to note that some of the endpoints in this trial appeared to approach—but did not reach—statistical significance. For example, the median interval to patient-reported alterations in taste was 2.3 weeks vs. 1.6 weeks in zinc-treated and placebo-exposed patients, respectively. The analysis of these differences generated a p value of 0.09. Furthermore, as described earlier, the rationale for studying zinc appeared sound, particularly in light of this mineral's purported role in wound repair and the maintenance of immunity (4–7). Because of this, we cannot rule out the possibility that zinc may be exerting some subtle protective effects on taste and that a much larger study might have been able to discern such effects. One must question, however, the clinical value of such a subtle contribution, should it exist.

Although this study was disappointing in its primary conclusion, it nonetheless allowed for some important observations on dysgeusia, two of which we discuss. First, this study provided a wealth of prospectively gathered data on altered taste during cancer therapy. Patients reported an absence of any taste; worsening taste with regard to bitterness, saltiness, sourness, and sweetness; and the development of a metallic taste. However, several other changes were noted that did not appear to be readily characterized using such descriptors. Some of these comments centered around a burning taste, a soapy taste, and an oily taste, as well as a variety of other unusual taste sensations. In short, the nature of taste alterations appears complex, and future research might strive to better understand these taste changes with which cancer patients are struggling.

Second, it has been assumed that alterations in taste negatively affect patients' global quality of life, but our study found no such association. The vivid description quoted earlier by MacCarthy-Leventhal illustrates that cancer patients find taste alterations distressing (2). However, it appears that patients are not so distressed that they manifest a "global" decline in quality of life. Somerfield (10) has distinguished the importance of focusing on disease- or condition-specific quality-of-life assessment—as opposed to "global" quality-of-life assessment (10). Future research might also focus on identifying quality-of-life parameters that are specific and highly relevant to cancer patients with dysgeusia.

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