

## Phase III Trial of an Emulsion Containing Trolamine for the Prevention of Radiation Dermatitis in Patients With Advanced Squamous Cell Carcinoma of the Head and Neck: Results of Radiation Therapy Oncology Group Trial 99-13

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### A B S T R A C T

#### Purpose

This multicentered phase III trial was designed to compare an emulsion containing trolamine against the usual supportive care within each participating institution for patients with head and neck cancer undergoing radiation therapy.

#### Patients and Methods

Patients with biopsy-proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were randomly assigned to one of the following treatments: prophylactic trolamine emulsion, interventional trolamine emulsion, or declared institutional preference. The primary outcome was the reduction in grade 2 or higher skin toxicity, as per National Cancer Institute Common Toxicity Criteria version 2.0. Secondary outcomes included patient-reported quality of life (QOL).

#### Results

From October 2000 to April 2002, 547 patients from 51 institutions were entered onto the trial. The average age was 59 years. Patients were predominately male (79%) and most continued to use tobacco products (52%). The rates of grade 2 or higher radiation dermatitis were 79%, 77%, and 79% in the prophylactic, interventional, and institutional preference arms of the study, respectively. No significant differences in QOL were found.

#### Conclusion

The results of this trial demonstrate no advantage for the use of trolamine in reducing the incidence of grade 2 or higher radiation dermatitis or improving patient-reported QOL. The use of 15 different local standards of care highlights the need to continue research that will result in evidence-based recommendations to reduce the burden of radiation dermatitis.

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### INTRODUCTION

Radiation therapy (RT) is a common treatment modality for patients with advanced squamous cell carcinoma of the head and neck. Trials of treatment intensification have suggested benefits for both the use of concurrent chemotherapy and accelerated fractionation regimens. As a consequence, treatment-related adverse events, including dermatitis, are an increasing concern. Dermatitis ranges from mild erythema to moist desquamation and ulceration of the skin. Severe reactions cause local discomfort, affecting patients' overall quality of life (QOL), and may lead to unplanned treatment delays, which could impact treatment effectiveness.

There is no recognized standard skin care for patients undergoing high-dose RT treatment. Natu-

ral gel,<sup>1</sup> topical vitamin C solution,<sup>2</sup> aloe vera gel,<sup>3</sup> dexpanthenol cream,<sup>4</sup> chamomile cream and almond ointment,<sup>5</sup> and topical cortisone cream<sup>6</sup> have not demonstrated consistent clinical benefits. More than 30 years of clinical experience with a trolamine emulsion has suggested efficacy in preventing and treating radiation-induced skin reactions.<sup>7</sup> Trolamine's mechanism of action seems to include the early recruitment of macrophages and the stimulation of granulation tissue.<sup>8</sup>

Recent trials have evaluated trolamine in the management of RT-induced dermatitis in women undergoing breast irradiation.<sup>9,10</sup> A phase III trial by the Radiation Therapy Oncology Group (RTOG), trial 97-13,<sup>9</sup> compared best supportive care with the prophylactic use of a trolamine emulsion and demonstrated a small advantage in a subset of women at

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particularly high risk of dermatitis. With generally higher rates of radiation dermatitis, patients undergoing RT for cancers of the head and neck seemed to be an ideal population to further investigate the potential benefits of trolamine therapy.

The current trial was designed to compare the use of trolamine emulsion, as a prophylactic agent and as an interventional agent, with declared institutional preference in reducing the incidence of higher grade radiation dermatitis. QOL changes were an important planned secondary outcome of the trial.

## PATIENTS AND METHODS

### Patient Population

All eligible patients we required to have biopsy-proven stage III or IV cancer of the oral cavity, oropharynx, hypopharynx, or larynx. Patients considered candidates for high-dose RT ( $\geq 50$  Gy) either as primary treatment or as postoperative treatment after surgical resection were eligible. Patients who were planned to receive concomitant boost fractionation or concurrent systemic chemotherapy were also eligible. Exclusion criteria included a poor performance status (Zubrod performance status of  $\geq 2$ ), pre-existing skin rash, ulceration or open wound in the treatment area, known allergy to trolamine, inflammatory or connective tissue disorder of the skin, and the planned use of amifostine. Skin assessments and QOL forms were completed before RT, weekly during RT, and weekly for 4 weeks after RT.

### Ethical Considerations

Before activation, each participating center was required to obtain research ethics board approval of the protocol and the local informed consent form and to provide a single institutional standard of care to be used throughout the trial. Informed consent was obtained from all patients, and signed copies of the consent form were provided to each patient.

### Treatment

All patients underwent simulation and RT planning. Radiation portals encompassed standard target volumes. After pretreatment evaluation and before initiating RT, patients were randomly assigned to one of the following three treatment arms: prophylactic trolamine emulsion, interventional trolamine emulsion, or declared institutional preference. Patients were stratified according to the planned RT dose (50 to 60 Gy *v* higher), nodal status (positive *v* negative), use of concurrent systemic therapy (yes *v* no), and radiation fractionation (standard *v* concomitant boost).

Patients on the prophylactic arm were instructed to apply trolamine three times daily beginning on the first day of RT, continuing throughout treatments, and for 2 weeks after treatment completion. Patients randomly assigned to the interventional arm were instructed to begin the application of trolamine only once their skin became itchy, bothersome, or reddened and to continue the application for 2 weeks after treatment completion. In both arms, trolamine was applied at 4-hour intervals. Patients were instructed to maintain at least a 4-hour interval between the application of trolamine and RT. They were also instructed to cleanse the treated area regularly with warm water and a mild soap and to pat the area dry gently with a cotton towel. This was suggested to prevent a buildup of the agent on the skin, which paradoxically could increase radiation dermatitis through an unintentional bolus effect. Bolus was permitted at the discretion of the treating physician. Trolamine use was discontinued immediately if an allergic reaction occurred or if grade 3 dermatitis was reported (an area  $> 1.5$  cm of confluent desquamation or bleeding in the treated area). Medix Pharmaceuticals (Americas Inc, Largo, FL) supplied all trolamine emulsion (Biafine) for this trial. Dispensed trolamine was recorded on the product log at each institution. On study completion, all unused product was returned to Medix Pharmaceuticals.

Patients randomly assigned to the standard arm received declared institutional preference or standard of care. In some institutions, the standard care was no specific intervention. Trolamine emulsion was not permitted as an institutional standard for the trial. If the usual institutional care was to apply

hydrocortisone cream for a grade 2 or greater radiation dermatitis, then this was permitted.

### Study Outcomes

Radiation dermatitis was assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0<sup>11</sup> and the Oncology Nursing Society<sup>12</sup> toxicity scoring system. QOL was measured using the Spitzer Quality of Life Index (SQLI)<sup>13</sup> and the Head and Neck Radiotherapy Questionnaire (HNRQ).<sup>14</sup> The SQLI is a validated patient self-assessment tool using a five-item categorical questionnaire summarized with a Likert scale. This form must have all questions answered to be assessable because response imputation is not possible. If the questionnaire was completed after the start of RT, it was not included in the analysis.

The HNRQ was specifically developed to measure RT-related acute morbidity and QOL from the perspective of head and neck patients treated with RT. It consists of 22 questions. Each question uses a 7-point Likert scale for responses, and scores range from 0 (no symptoms) to 6 (worst symptoms). A higher score indicates greater toxicity and a poorer QOL. The worst possible score is 132. The questions relate to the following six domains: oral cavity (mouth), throat, skin, digestive function, energy, and psychosocial. The skin domain was of specific interest in this study. The three specific skin questions measure dryness of the skin, itching of the skin, and pain or soreness of the skin.

### Statistical Methods

The study was designed to detect a 33% reduction in the incidence of grade 2 or higher skin toxicity with the prophylactic use of trolamine. Standard measures of  $\alpha$  (.05) and statistical power (0.90) were used with a two-sided test design for sample size calculations. With a 10% inflation factor incorporated for anticipated patient ineligibility or inassessability, 166 patients per arm were required. The highest grade of radiation dermatitis reported was compared across the treatment arms using a  $\chi^2$  test. On the basis of the results of the previous RTOG breast trial, a subset analysis based on smoking status was planned.<sup>9</sup> The burden of skin toxicity from the NCI-CTC scale was calculated as area under the curve (AUC) using all patients with at least two toxicity assessments during the 10-week assessment period. The AUC value for each patient was calculated using the grade of skin toxicity on the vertical scale and the time of the assessment on the horizontal scale. Patient AUC values were used to calculate an average toxicity score for each treatment arm.

## RESULTS

A total of 547 patients were accrued from October 2000 to April 2002. Fifty-one RTOG institutions across North America participated in the study. Forty-one patients were excluded (17 on the prophylactic arm, seven on the interventional arm, and 17 on the institutional standard arm), so that a total of 506 patients were used for the primary end point analysis. Thirty-nine patients were ineligible (one with skin ulceration, three with incorrect Zubrod, three withdrew consent, one improperly consented, four with recurrent disease, eight with incorrect diagnosis, three with incorrect staging, and 16 using amifostine), and two patients were cancelled (one withdrew from study and one was from a non-RTOG institution). There remained 166 patients on the prophylactic trolamine arm, 175 patients on the interventional trolamine arm, and 165 patients on the institutional preference arm.

The characteristics of the patients before random assignment were well balanced and are listed in Table 1. The average patient age was 59 years, and 79% of the patients were male. Eighty-four percent of the sample size was white, and 11% were African American. Fifty-two percent of patients continued to smoke. The oropharynx was the most prevalent tumor site (45% of patients). The majority of patients (59%) had T3 or T4 disease, and 75% had involved lymph nodes.

**Table 1.** Baseline Characteristics

Characteristic	Prophylactic Trolamine (n = 166)		Interventional Trolamine (n = 175)		Institutional Preference (n = 165)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Mean age, years	59.1		59.5		58.8	
Male	128	77	136	78	136	82
Race/ethnicity						
White	140	84	144	82	140	85
African American	19	12	20	11	17	10
Hispanic	5	3	8	5	4	2
Other	1	1	3	2	4	2
Origin of tumor						
Oropharynx	81	49	76	43	71	43
Larynx and epiglottis	38	23	45	26	53	32
Oral cavity	37	22	38	22	31	19
Hypopharynx	10	6	16	9	10	6
Tumor stage						
T0	1	1	0	0	1	1
T1	24	14	18	10	19	12
T2	43	26	52	30	50	30
T3	53	32	55	31	53	32
T4	45	27	50	29	42	25
Node stage						
N0	46	28	40	23	41	25
N1	34	20	31	18	36	22
N2	74	45	93	53	80	48
N3	11	7	11	6	8	5

Institutional preference was recorded at study registration. Fourteen different products were reported as standard treatment. In less than 2% of patients, the product used was unknown because the form was not completed. No specific active therapy was the declared standard institutional policy for two patients on the institutional preference arm of the trial. Used products were categorized into gels, creams, corticosteroids, Aquaphor (USA Beiersdorf Inc, Wilton, CT), and other (Table 2). The most common product used was Aquaphor, which was the institutional preference for 39% of the patients. No significantly different outcomes were found for any of the categories of standard care products (gel *v* cream *v* steroids *v* Aquaphor; data not shown).

Approximately 80% of the patients received an RT dose greater than 60 Gy (Table 3), and 95% of patients completed RT. Fifty-three percent of patients on the study received combined-modality treatment. Concomitant boost was used to treat 93% of the patients. There was a slightly higher rate of treatment breaks as a result of toxicity in the institutional arm compared with both trolamine arms for current and former smokers, but the breaks were, on average, shorter.

**Table 2.** Product Preference

Product	Institutional Preference (n = 165)	
	No. of Patients	%
Gel	39	24
Cream	26	16
Corticosteroid	18	11
Aquaphor	65	39
Other	17	10

The primary end point was to compare the incidence of grade 2 or higher radiation dermatitis. As summarized in Table 4, the three arms of the trial reported rates of grade 2 or higher radiation dermatitis of 79%, 77%, and 79% for the prophylactic, interventional, and institutional preference arms, respectively; rates of grade 3 or 4 dermatitis did not differ, with rates of 25%, 25%, and 23% in the three arms, respectively. The Oncology Nursing Society toxicity score reported a small to moderate amount of moist desquamation in 31%, 28%, and 34% of patients on the prophylactic, interventional, and institutional

**Table 3.** Treatment Characteristics

Characteristic	Prophylactic Trolamine (n = 163)		Interventional Trolamine (n = 175)		Institutional Preference (n = 160)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
> 60 Gy total dose	124	78	140	81	134	86
RT completed	153	94	168	96	153	96
Concurrent chemotherapy	86	53	92	53	82	51
Concomitant boost	149	91	163	93	147	92
RT incomplete, refusal	2		0		1	
RT incomplete, progression	0		0		1	
RT incomplete, death	1		3		1	
RT incomplete, toxicity	0		0		1	
No RT, refusal	1		0		0	
No RT, illness	1		0		0	
No RT, death	1		0		0	
No RT delivery data	1		4		0	

Abbreviation: RT, radiation therapy.

**Table 4.** Maximum Skin Toxicity

Toxicity	Prophylactic Trolamine (n = 163)		Interventional Trolamine (n = 172)		Institutional Preference (n = 159)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
<b>NCI-CTC criteria*</b>						
None	5	3	3	2	2	1
Faint erythema or dry desquamation	30	18	36	21	31	20
Moderate to brisk erythema	88	54	90	52	90	57
Confluent moist desquamation	35	21	33	19	31	20
Skin necrosis or ulceration	5	3	10	6	5	3
<b>ONS criteria†</b>						
No changes noted	5	3	3	2	2	1
Faint or dull erythema	26	16	23	13	23	14
Bright erythema	25	15	33	19	26	16
Dry desquamation with or without erythema	42	26	42	24	42	26
Small to moderate amount of moist desquamation	51	31	48	28	52	34
Confluent moist desquamation	11	7	17	10	13	8
Ulceration, hemorrhage, or necrosis	3	2	6	3	1	1

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; ONS, Oncology Nursing Society.

\* $P = .82$ .

† $P = .86$ .

preference arms, respectively. Confluent moist desquamation was observed in 7%, 10%, and 8% of patients on the prophylactic, interventional, and institutional preference arms, respectively; ulceration, hemorrhage, or necrosis was experienced in 2%, 3%, and 1% of patients in the three arms, respectively. The mean AUC was the same for all three arms (AUC = 1.1; institutional preference  $\nu$  prophylactic trolamine,  $P = .65$ ; institutional preference  $\nu$  interventional trolamine,  $P = .85$ ). All assessments performed over the 10-week evaluation period were used to provide an average toxicity score. There were no significant differences between the treatment arms with any of these measures. Subset analysis was performed based on smoking status, but no significant differences were found between patients who had never smoked, former smokers, and current smokers.

An amended analysis was conducted at the request of the sponsor to determine whether there was an association between the number of trolamine emulsion tubes dispensed and degree of toxicity experienced. Eighty-four percent and 80% of the product logs were submitted for the prophylactic and interventional arms, respectively. One to three tubes were dispensed to 37% and 48% of patients and 8 to 20 tubes were dispensed to 26% and 15% of patients on the prophylactic and interventional arms, respectively. There was no difference in maximum toxicity reported with increasing number of tubes dispensed. At 4 weeks after treatment, the presence of ongoing dermatitis was dichotomized as subsided or not. No association was found on either of the trolamine arms between amount of dispensed trolamine and ongoing dermatitis ( $P = .36$  for prophylactic arm and  $P = .31$  for interventional arm).

QOL was a planned secondary end point of the study. Across treatment arms, between 83% and 90% of patients completed the baseline QOL assessments. Results from 425 patients (SQLI) and 444 patients (HNRQ), with evaluations completed before RT and at treatment completion, were used in the QOL analysis.

There was no overall difference detected between arms by the two QOL instruments. The results of the SQLI were consistent with assigned measures of skin toxicity; patients with grade 3 or 4 toxicity had

the worst measures of QOL. There was no apparent association between smoking status and the SQLI QOL scores. The HNRQ has no published reliability estimates, and for intraindividual change, a 20% change in score was considered clinically significant. Table 5 lists the end of RT HNRQ scores, indicating no significant difference between the three arms overall ( $P = .38$ ) or, specifically, in the skin subscale of the HNRQ ( $P = .30$ ) at treatment completion. As with the SQLI, Table 5 demonstrates consistency between the skin subscale of the HNRQ and reported skin toxicity as per the NCI-CTC.

## DISCUSSION

This randomized trial was designed to compare trolamine, both as a prophylaxis and as an intervention, with usual supportive care for patients with head and neck cancer undergoing RT. The study accrued well across a number of institutions, enhancing the generalizability of

**Table 5.** End of Radiotherapy Head and Neck Radiotherapy Questionnaire

Measure	Prophylactic Trolamine	Interventional Trolamine	Institutional Preference
<b>Total score*</b>			
No. of patients	119	135	109
Mean	49.0	53.6	52.1
Median	49	53	53
Range	0-110	2.5-122	0-118
<b>Skin score†</b>			
No. of patients	143	157	130
Mean	4.8	5.3	5.7
Median	3	4	5
Range	0-18	0-18	0-18

\*Maximum score for total score is 132;  $P = .38$  for total score.

†Maximum score for skin score is 18;  $P = .30$  for skin score.

the trial results. The variety of recorded institutional preferences reflects the lack of high-quality evidence supporting a standard treatment approach for the care of patients with or at risk of developing radiation dermatitis. Presently, creams, gels, corticosteroids, and Aquaphor are commonly used without any suggestion from the present trial that any one approach is clinically superior to any other.

This study did not demonstrate a benefit for the use of prophylactic or interventional trolamine over the range of commonly used institutional products. This lack of benefit was consistent across the spectrum of investigator- and patient-derived measures used as primary and secondary end points. Unfortunately, this is consistent with other phase III trials that have attempted to evaluate the role of trolamine. Although the quality of existing reports can be debated,<sup>15-17</sup> the inability to detect a meaningful benefit must be recognized. A recent Continuing Education Review by Wickline<sup>16</sup> in the Oncology Nursing Forum highlights these issues.

Perhaps we are asking the wrong question regarding the possible benefits of trolamine. A recently published study<sup>18</sup> involving human skin cell lines demonstrated a benefit of trolamine on the vascular parameters of the dermis. Application of trolamine to human skin cells reduced vasodilatation, reduced dermal edema, and seemed to increase epithelial cell proliferation. Initially, trolamine emulsion was developed as a therapeutic agent for use on thermal burns, suggesting that the true benefit may come from the accelerated repair of more seriously damaged skin. Trolamine may be more beneficial for patients who have developed grade 3 or 4 RT-induced dermatitis because it may facilitate improved healing times. Grade 3 or 4 radiation dermatitis occurred in approximately 25% of this patient population. In this trial, once this level of toxicity occurred, all trolamine and protocol treatment was discontinued.

A potential limitation of this trial was the absence of patient diaries to record compliance with application directions, the timing

and number of applications, and the full amount of product used. Product logs from the centers were used as a surrogate for such detail. In future skin care trials, the use of detailed patient dairies may be warranted. The product log used for this trial was simply a record of the number of tubes supplied to each participant and did not necessarily measure compliance. In support of the results, however, the current trial likely provided patients with more detailed application instructions than they would have otherwise received, and still no significant clinical benefit was demonstrated. Additionally, the study was not blinded or placebo controlled, which at least introduces the possibility that skin grading and QOL assessments may be subject to reviewer and patient bias.

The impact of RT-induced skin dermatitis is an important issue for all health care professionals treating head and neck cancer patients to appreciate. The link between reported levels of dermatitis and patient QOL scores was well documented in this trial. Large multicenter trials to further evaluate strategies to reduce the burden of radiation dermatitis must continue in an effort to improve overall patient care.

The trend to treat patients with combined chemotherapy and RT using higher doses has led to an increased incidence of high-grade radiation dermatitis. The rate of radiation dermatitis reported in the RTOG 90-03<sup>19</sup> phase III study, which evaluated four differing fractionation regimens for patients with stages III and IV head and neck cancer, was 48%, 7.4%, and 0% for grades 2, 3, and 4 dermatitis, respectively. In the present trial, the average rates of radiation dermatitis were 54%, 20%, and 4% for grades 2, 3, and 4, respectively. Despite attempts to improve skin care and reduce skin reactions, patients are experiencing more RT-induced dermatitis with the frequent use of accelerated RT schedules and chemotherapy, as was delivered to the majority of patients in this trial. Further studies to improve management of patients experiencing radiation dermatitis are warranted.

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### **Authors' Disclosures of Potential Conflicts of Interest**

The authors indicated no potential conflicts of interest.

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