

Washington University School of Medicine

Digital Commons@Becker

Open Access Publications

2-1-2018

Phase 1b/2a trial of the superoxide dismutase mimetic GC4419 to reduce chemoradiotherapy-induced oral mucositis in patients with oral cavity or oropharyngeal carcinoma

Carryn M Anderson
University of Iowa

Stephen T Sonis
Dana-Farber Cancer Institute

Christopher M Lee
Cancer Care Northwest

Douglas Adkins
Washington University School of Medicine in St. Louis

Bryan G Allen
University of Iowa

See next page for additional authors

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Please let us know how this document benefits you.

Recommended Citation

Anderson, Carryn M; Sonis, Stephen T; Lee, Christopher M; Adkins, Douglas; Allen, Bryan G; Sun, Wenqing; Agarwala, Sanjiv S; Venigalla, Madhavi L; Chen, Yuhchay; Zhen, Weining; Mould, Diane R; Holmlund, Jon T; Brill, Jeffrey M; and Buatti, John M, "Phase 1b/2a trial of the superoxide dismutase mimetic GC4419 to reduce chemoradiotherapy-induced oral mucositis in patients with oral cavity or oropharyngeal carcinoma." *International journal of radiation oncology, biology, physics.* 100, 2. 427 - 435. (2018). https://digitalcommons.wustl.edu/open_access_pubs/8159

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.

Authors

Caryn M Anderson, Stephen T Sonis, Christopher M Lee, Douglas Adkins, Bryan G Allen, Wenqing Sun, Sanjiv S Agarwala, Madhavi L Venigalla, Yuhchyan Chen, Weining Zhen, Diane R Mould, Jon T Holmlund, Jeffrey M Brill, and John M Buatti

Clinical Investigation

Phase 1b/2a Trial of the Superoxide Dismutase Mimetic GC4419 to Reduce Chemoradiotherapy-Induced Oral Mucositis in Patients With Oral Cavity or Oropharyngeal Carcinoma



Carryn M. Anderson, MD,* Stephen T. Sonis, DMD, DMSc,[†]
Christopher M. Lee, MD,[‡] Douglas Adkins, MD,[§]
Bryan G. Allen, MD, PhD,* Wenqing Sun, MD, PhD,*
Sanjiv S. Agarwala, MD,^{||} Madhavi L. Venigalla, MD,[¶]
Yuhchyan Chen, MD, PhD,[#] Weining Zhen, MD,**
Diane R. Mould, PhD,^{††} Jon T. Holmlund, MD,^{‡‡} Jeffrey M. Brill, BS,^{‡‡}
and John M. Buatti, MD*

*Department of Radiation Oncology, University of Iowa Hospitals and Clinics, Iowa City, Iowa;
[†]Biomodels and Division of Oral Medicine, Dana-Farber Cancer Institute, Boston, Massachusetts;
[‡]Cancer Care Northwest, Spokane, Washington; [§]Section of Medical Oncology, Washington University
School of Medicine, St. Louis, Missouri; ^{||}Department of Medical Oncology, St. Luke's University
Hospital and Temple University, Easton, Pennsylvania; [¶]Lakeland Regional Health Cancer Center,
Lakeland, Florida; [#]Department of Radiation Oncology, Wilmot Cancer Institute, University of
Rochester, Rochester, New York; **Department of Radiation Oncology, University of Nebraska
Medical Center, Omaha, Nebraska; ^{††}Projections Research Inc., Phoenixville, Pennsylvania; and
^{‡‡}Galera Therapeutics, Inc., Malvern, Pennsylvania

Received Aug 3, 2017, and in revised form Sep 26, 2017. Accepted for publication Oct 10, 2017.

Summary

Severe oral mucositis is a critical problem in patients

Purpose: To assess the safety of the superoxide dismutase mimetic GC4419 in combination with radiation and concurrent cisplatin for patients with oral cavity or oropharyngeal cancer (OCC) and to assess the potential of GC4419 to reduce severe oral mucositis (OM).

Reprint requests to: Carryn M. Anderson, MD, Department of Radiation Oncology, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, 01614 PFPW, Iowa City, IA 52242. Tel: (319) 353-8836; E-mail: carryn-anderson@uiowa.edu

The results of this study were presented in part at the Multidisciplinary Head and Neck Cancer Symposium (oral presentation), February 18-20, 2016, Scottsdale, AZ; the American Society of Clinical Oncology Annual Meeting (poster discussion), June 3-7, 2016, Chicago, IL; and the 58th Annual Meeting of the American Society for Radiation Oncology (oral presentation), September 24-28, 2016, Boston, MA.

This study was funded by Galera Therapeutics, Inc.

Conflict of interest: J.M.Br and J.T.H are employees of Galera Therapeutics, Inc and holders of stock options.

Acknowledgments—The authors thank Charles Kunos, MD, PhD, and Larisa Greenberg, MD, for their contributions to patient enrollment; Curtis Miyamoto, MD, for providing independent review of the intensity modulated radiation therapy plans for enrolled patients; the Free Radical and Radiation Biology Research Core at University of Iowa for sample preparation and handling; Robert Beardsley and Art Fratamico for their helpful comments about the manuscript; and Gareth Smith for his assistance in preparing the manuscript.

receiving chemoradiation for oral cavity and oropharynx cancer. This phase 1/2 dose and duration escalation study tested the safety of a daily 60-minute pre-RT infusion of GC4419, a superoxide dismutase mimetic. A maximum tolerated dose was not reached, safety was acceptable (nausea/vomiting and facial paresthesia during infusion appeared GC4419 dose-related), and doses of 30 and 90 mg/d for the duration of radiation were selected for further study.

Patients and Methods: Patients with locally advanced OCC treated with definitive or postoperative intensity modulated radiation therapy (IMRT) plus cisplatin received GC4419 by 60-minute intravenous infusion, ending <60 minutes before IMRT, Monday through Friday for 3 to 7 weeks, in a dose and duration escalation study. Oral mucositis was assessed twice weekly during and weekly after IMRT.

Results: A total of 46 patients received GC4419 in 11 separate dosing and duration cohorts: dose escalation occurred in 5 cohorts receiving 15 to 112 mg/d over 3 weeks (n = 20), duration escalation in 3 cohorts receiving 112 mg/d over 4 to 6 weeks (n = 12), and then 3 additional cohorts receiving 30 or 90 mg/d over 6 to 7 weeks (n = 14). A maximum tolerated dose was not reached. One dose-limiting toxicity (grade 3 gastroenteritis and vomiting with hyponatremia) occurred in each of 2 separate cohorts at 112 mg. Nausea/vomiting and facial paresthesia during infusion seemed to be GC4419 dose-related. Severe OM occurred through 60 Gy in 4 of 14 patients (29%) dosed for 6 to 7 weeks, with median duration of only 2.5 days.

Conclusions: The safety of GC4419 concurrently with chemoradiation for OCC was acceptable. Toxicities included nausea/vomiting and paresthesia. Doses of 30 and 90 mg/d administered for 7 weeks were selected for further study. In an exploratory analysis, severe OM seemed less frequent and briefer than expected. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Oral mucositis (OM) is a common, disruptive, and painful complication of radiation and chemoradiation (CRT) for head and neck squamous cell carcinoma (HNSCC) (1). Approximately 70% of patients receiving CRT for oral cavity or oropharyngeal cancer (OCC) develop severe OM, defined as grade 3 to 4 by the World Health Organization (WHO) scale (2, 3). Oral mucositis causes marked pain requiring narcotic analgesics and adversely affects nutrition, hydration, speech, swallowing, quality of life, bacteremia risk, and feeding tube placement and use rates (4, 5). Severe OM is also associated with radiation treatment breaks, which harms successful tumor management (6-8). The financial cost of managing patients with severe OM is substantial and is attributable to increased hospitalization and emergency room use (9, 10).

Recommended approaches to managing OM are limited to palliation and pain control with topical agents and systemic analgesics (11-19). The only approved drug or biological to reduce OM, palifermin, is limited to patients at risk for OM associated with conditioning regimens before stem cell transplant for the treatment of hematologic malignancies (20, 21).

The pathogenesis of mucositis is a complex sequence of biologic events in which oxidative stress plays a pivotal initiating role (22). Therapeutic radiation causes radiolytic hydrolysis and the formation of reactive oxygen species, including superoxide anion ($O_2^{\bullet-}$). Superoxide is extremely reactive, triggering a cascade of signaling pathways in the cells and tissues of the submucosa and resulting in apoptosis of epithelial stem cells, consequent loss of epithelial renewal, atrophy, and mucosal ulceration (23).

A complement of naturally occurring superoxide dismutase (SOD) enzymes exists to dispose of superoxide (24). However, large, rapidly produced amounts of superoxide due to therapeutic radiation can overwhelm these native SOD enzymes. GC4419 is a highly stable manganese-containing macrocyclic complex (molecular weight = 483), whose activity mimics the native enzymes, selectively removing superoxide anions without reacting with other reactive oxygen species, including nitric oxide, hydrogen peroxide, and peroxynitrite. An active enantiomer of GC4419 protected mice from lethal total body irradiation (25) and reduced radiation-induced OM in a hamster cheek pouch model in a dose-related fashion (26). GC4419 had equivalent effects in the same OM model but did not spare tumor from the effects of CRT in multiple preclinical models (Galera Therapeutics, unpublished data). Further, GC4419 protected mice from radiation-induced pulmonary fibrosis (27).

The present study was done to assess the safety of GC4419 in combination with radiation and concurrent cisplatin for patients with OCC and to assess the potential of GC4419 to reduce severe OM.

Patients and Methods

Patients

Eligible patients had oral cavity or oropharyngeal, stage III-IVb HNSCC, Eastern Cooperative Oncology Group performance status ≤ 2 , and a treatment plan that called for standard fractionation intensity modulated radiation therapy (IMRT) with concurrent cisplatin (80-100 mg/m² every 3 weeks or

30–40 mg/m² weekly). The IMRT plan had to include at least 2 oral mucosal sites (right or left buccal mucosa, right or left ventral/lateral oral tongue, floor of mouth, or soft palate) within the cumulative 50-Gy isodose line. The IMRT plans were centrally reviewed by an independent radiation oncologist to confirm adherence to protocol requirements. Adequate marrow, renal, and hepatic functions were required. Prophylactic percutaneous endoscopic gastrostomy tube placement was allowed at enrollment. Patients were excluded if they had prior induction chemotherapy, significant dietary compromise due to reduced oral/pharyngeal function, or concurrent treatment with nitrates.

The protocol was approved by each institution's institutional review board and was registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov). Investigators obtained written informed consent from each participant. Data were anonymized to protect the study subjects' identities.

Treatment and study design

Intensity modulated radiation therapy was administered once daily, Monday-Friday, at 2.0 to 2.2 Gy/d, to a cumulative tumor dose between 60 and 72 Gy. The assigned dose of GC4419 was delivered intravenously in normal saline over 60 minutes, ending within 60 minutes before each radiation fraction. Oral rinses limited to sodium bicarbonate, lidocaine, and antifungal agents were permitted. Other concurrent available or experimental systemic or topical pharmaceuticals or devices, or low-level laser therapy, were excluded. Supportive care per American Society of Clinical Oncology guidelines, including antiemetic drugs for cisplatin, was encouraged.

The study followed a serial cohort dose-escalation design with 3 to 6 patients enrolled per cohort. The first 5 cohorts received GC4419 before each of the first 14 IMRT fractions (over approximately 3 weeks), reflecting the duration of Investigational New Drug Application-supporting animal toxicology studies of GC4419. These 5 serial cohorts received 15, 30, 50, 75, or 112 mg of GC4419 per dose. These doses were based on previous results with a single 15-minute infusion administered to healthy human volunteers; the 60-minute infusion duration was chosen because dogs tolerated higher doses administered more slowly (ie, 12.5 mg/kg over 60 minutes vs 5 mg/kg over 15 minutes [Galera Therapeutics, unpublished observation]). On the basis of observed safety results in the first 5 cohorts, the protocol was then amended to allow "duration extension" of GC4419 administered progressively longer during IMRT. Three serial cohorts received 112 mg of GC4419 before IMRT for 4, 5, or 6 weeks. Subsequent review of safety and OM results through these cohorts led to a decision by the sponsor to add 3 cohorts to extend dosing further at reduced doses: 90 mg for 6 or 7 weeks or 30 mg for 7 weeks.

Dose-limiting toxicity (DLT) was defined as follows: grade 3 or 4 nausea or vomiting despite maximal antiemetic

therapy; grade 4 anemia; grade 4 thrombocytopenia or grade 3 associated with hemorrhage; grade 4 neutropenia lasting >7 days; grade 3 or 4 febrile neutropenia; or other grade 3+ events (except oral mucositis), judged by the investigator not attributable to IMRT, cisplatin, or complications of HNSCC. For adverse events attributable to IMRT or cisplatin but judged to be exacerbated by the presence of GC4419, dose modification of GC4419 was at the investigator's discretion. For any given patient, DLT required the GC4419 dose to be reduced 1 dose level (ie, from 112 mg to 75 mg). Up to 2 such dose reductions per patient were permitted. Six patients per cohort were enrolled if DLT was observed in 1 of the first 3 patients. The maximum tolerated dose (MTD) of GC4419 was defined as the highest dose and longest schedule at which DLT was observed in >1 patient in a single dose and schedule cohort.

Study assessments and analysis

Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Oral mucositis was assessed by trained investigator-evaluators using WHO criteria, in which grade 0 = no mucositis; grade 1 = pain and erythema; grade 2 = ulceration, able to eat solid food; grade 3 = ulceration, able to consume only liquids; grade 4 = ulceration, inability to eat requiring tube or parenteral feeding. Oral mucositis was assessed twice weekly with at least a 48-hour interval between assessments during IMRT and weekly thereafter for up to 8 weeks or until the WHO score was <2. Oral mucositis assessment training and quality control were performed by Clinical Assistance Programs (Framingham, MA) to ensure that (1) all oral assessments were performed in a consistent manner using standardized questions, oral cavity examination technique and order, and data collection; and (2) WHO grade scoring was correctly assigned per assessment findings for all OM assessments. To reduce the variability in assessing a patient's diet, investigator-evaluators were trained to carefully elucidate whether dietary compromise was due to oral pain. If not, and the diet was compromised by confounding factors (eg, dysgeusia, edentulous, nausea, mucus, throat pain, functional dysphagia), the WHO score was determined according to what the patient said he or she could eat absent these confounding factors.

Plasma concentrations of GC4419 and major metabolites were measured, using a validated liquid chromatography/mass spectrometry method, before infusion, at the end of infusion, and 1, 2, 4, and 6 to 8 hours after infusion with 2 dosing cycles: week 1/day 2, and day 3 during the last week of the infusion schedule.

Tumor status was assessed by clinical examination at the end of IMRT and 3, 6, 9, and 12 months thereafter. Standard-of-care imaging (computed tomography, positron emission tomography, or magnetic resonance imaging) was

done before and 3 and 12 months after IMRT. After completion of the 12-month assessment, study follow-up ended.

Statistical analysis of clinical endpoints was descriptive. Severe OM incidence, time to onset, and duration were tabulated. Patients who never developed OM grade >2 had values of 0 days and >50 days imputed for duration and onset, respectively, of severe OM. Pharmacokinetics were analyzed by noncompartmental analysis using the software program Phoenix (WinNonlin Professional version 6.4; PharSight, Mountain View, CA).

Results

Nine US centers enrolled 46 patients between August 2013 and June 2015. Patient characteristics are summarized in [Table 1](#). Forty-three patients completed OM assessments and were considered evaluable for OM; 44 completed tumor follow-up through 1 year after IMRT and were evaluable for tumor endpoints ([Table 2](#)).

Safety

Initial cohorts received GC4419 for the first 14 days of IMRT at 15 mg (n=4), 30 mg (n=3), 50 mg (n=4), 75 mg (n=3), or 112 mg (n=6). In these 5 cohorts, 1 toxicity event—grade 3 nausea occurring at 112 mg—was considered potentially drug-related and therefore dose limiting.

Table 1 Patient characteristics

Characteristic	Number
Total patients enrolled	46
Men/women	38/8
Age (y), median (range)	58.5 (37-81)
Primary tumor	
Oral cavity	7
Oropharyngeal	38
Unknown	1
Postoperative/definitive treatment	18/28
Overall stage	
III	2
IVA	39
IVB	4
Not available	1
Tumor HPV status	
Positive	25
Negative	2
Not available	19
Cisplatin schedule	
Every 3 wk	39
Weekly	7
Evaluable for OM assessment	43
Evaluable for tumor follow-up	44

Abbreviations: HPV = human papillomavirus; OM = oral mucositis.

Values are number unless otherwise noted.

Table 2 Distribution of patients by dose cohort

Dose cohort	No. enrolled	No. evaluable for safety	No. evaluable for OM	No. evaluable for recurrence
15 mg/d × 14 doses	4	4	4	4
30 mg/d × 14 doses	3	3	3	3
50 mg/d × 14 doses	4	4	4	4
75 mg/d × 14 doses	3	3	3	3
112 mg/d × 14 doses	8	8	6*	6*
112 mg/d × 20 doses	3	3	3	3
112 mg/d × 25 doses	3	3	3	3
112 mg/d × 30 doses	5	5	3 [†]	5
90 mg/d × 30 doses	3	3	4 [‡]	3
90 mg/d × 35 doses	6	6	6	6
30 mg/d × 35 doses	4	4	4	4
Totals	46	46	43	44

Abbreviation as in [Table 1](#).

* Two patients enrolled at 112 mg × 14 doses withdrew early, and two additional patients were enrolled in that cohort to complete safety and efficacy analysis.

[†] One patient was analyzed with the 90 mg/d × 30 doses cohort and 1 patient limited OM evaluation to once weekly and thus was excluded from OM analysis.

[‡] One patient enrolled at 112 mg/d × 30 doses actually received 87 mg/d, per protocol provision, and is included with others at 90 mg/d × 30 doses in OM analysis.

Ten of the 20 patients in these 5 cohorts completed treatment with no severe OM ([Fig. 1](#)). On the basis of the favorable tolerability profile of GC4419 in these cohorts, GC4419 dosing duration was extended by protocol amendment, initially in 3 serial cohorts at 112 mg—20 doses/4 weeks, 25 doses/5 weeks, or 30 doses/6 weeks (n=3 each). In these 3 cohorts, one patient in the 112 mg/6 weeks cohort had grade 3 nausea, which was considered dose limiting. Because no single cohort had >1 patient with DLT, the MTD was not considered exceeded. However, to reduce the potential risk of nausea, the GC4419 dose was lowered in the next 2 additional cohorts, to 90 mg for 30 doses/6 weeks (n=4), and then 35 doses/7 weeks (n=6). Concurrently, another cohort received 30 mg for 35 doses/7 weeks (n=4).

Of 46 patients, 41 (89%) received all planned GC4419 infusions. Five patients, all at 112 mg, stopped GC4419 early for adverse events (n=2) or patient request (n=3), receiving 2 of 14, 3 of 14, 9 of 14, 10 of 30, or 26 of 30 infusions. One additional patient (112 mg × 30 doses) had a permanent reduction to 75 mg for the last 6 doses

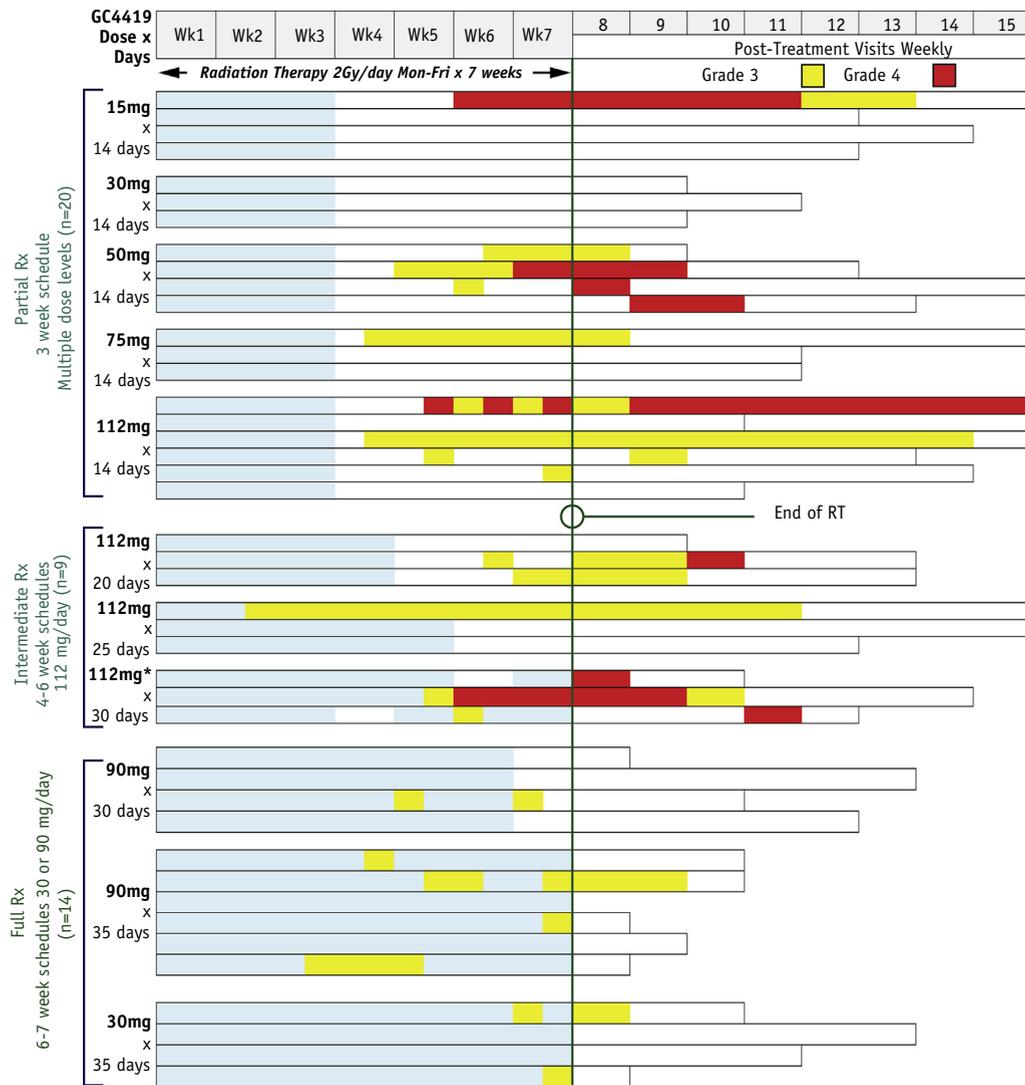


Fig. 1. Swimmers' plot of oral mucositis scores for each evaluable patient (n=43) over time, stratified by the 3 dosing duration groups. Each horizontal bar (lane) provides World Health Organization scores for an individual patient during the period of chemoradiotherapy (weeks 1-7) and after chemoradiotherapy (weeks 8-15, top of figure). Severe oral mucositis grade 3 is denoted by yellow shading and grade 4 by red. Light blue within a lane denotes administration of GC4419. * One patient enrolled at 112 mg × 30 doses received 87 mg per protocol and is summarized with the 90 mg × 30 dose cohort in this figure.

because of grade 3 nausea; the other 40 received their full doses.

The median total radiation therapy dose was 70 Gy (<10 Gy for 2 early-withdrawing patients, 81.3 Gy for 1 patient, 66-70 Gy for all others). Radiation therapy breaks of 5 or more consecutive fractions occurred in 3 of 46 patients (6.5%) (attributed to grade 3 nausea; respiratory failure unrelated to GC4419; patient noncompliance). A total of 9 patients (1 at 15 mg of GC4419, 2 at 30 mg, 3 at 90 mg, 3 at 112 mg), all receiving every-3-week platinum, had their platinum doses reduced by 20% to 60% for the second and/or third scheduled dose, at the discretion of the treating investigator, because of adverse events attributed to cisplatin. Four of the 9 patients received the full schedule of

GC4419 (1 30 mg/d × 35 doses, 2 90 mg/d × 35 doses, and 1 90 mg/d × 30 doses), and another 3 of the 9 patients received 112 mg/d (1 × 14 doses, 1 × 20 doses, and 1 × 30 doses).

Overall, adverse events, the most common of which were cytopenias, nausea, fatigue, constipation, dysgeusia, and dry mouth, were considered attributable to IMRT/cisplatin, complications of HNSCC, or other concomitant conditions. Although dose escalation of GC4419 was curtailed before reaching a formal MTD, grade 3 nausea or vomiting was more frequent at higher GC4419 doses (Table 3), as was transient, infusion-related grade 1 facial paresthesia that spontaneously resolved shortly after the infusion and did not limit dosing.

Table 3 Adverse events of note

Parameter	15 mg daily		30 mg daily		50 mg daily		75 mg daily		90 mg daily		112 mg daily			
	14 total doses	14 total doses	35 total doses	14 or 35 total doses	14 total doses	14 total doses	30 total doses	35 total doses	30 or 35 total doses	14 total doses*	20 total doses	25 total doses	30 total doses*	14, 20, 25, or 30 total doses
N	4	3	4	7	4	3	4	6	10	8	3	3	4	18
Paresthesia (grade 1)	0	0	1 (25)	1 (14)	1 (25)	0	2 (50)	3 (50)	5 (50)	5 (63)	1 (33)	1 (33)	4 (100)	11 (61)
Nausea (grade 3)	0	0	0	0	0	0	0	2 (33)	2 (20)	2 (25)	0	1 (33)	1 (25)	4 (22)
Vomiting (grade 3)	0	0	1 (25)	1 (14)	0	0	0	1 (16)	1 (10)	2 (25)	0	1 (33)	1 (25)	4 (22)
Nausea (any grade)	4 (100)	2 (67)	4 (100)	6 (86)	4 (100)	2 (67)	3 (75)	6 (100)	9 (90)	6 (75)	2 (67)	3 (100)	4 (100)	15 (83)

Values are number (percentage). Tabulated events are listed without regard to attribution to GC4419.

* A total of 5 patients—3 in the 112 mg/14 dose cohort, and 2 in the 112 mg/30 dose cohort—received fewer infusions than planned, and 1 in the 112 mg/30 dose cohort had a permanent dose reduction to 75 mg. Also, one patient enrolled at 112 mg × 30 doses received 87 mg per protocol and is summarized with the 90 mg × 30 dose cohort in this table. See text.

OM efficacy

For patients who received 30 or 90 mg over the full 6 to 7 weeks of CRT, the cumulative incidence of severe OM was 29% (4 of 14) through 6 weeks of RT (60 Gy), and 50% (7 of 14) at any time, with a median time to onset >50 days, and a median duration of 2.5 days (Fig. 1, Table 4). In contrast, in the initial 5 cohorts, GC4419 for 3 weeks was not as effective in reducing cumulative severe OM through 60 Gy (incidence 40% and duration 4.5 days). For patients in the intermediate treatment group, cumulative incidence at 60 Gy was 44%, at any time 67%, median onset 43 days, and duration 18 days. Duration of all grades of OM seemed to be shorter as GC4419 administration was extended further in the IMRT treatment period (Fig. 2).

Pharmacokinetics

Peak concentration and area under the concentration time profile were approximately dose-proportional for GC4419

in plasma (data not shown). The terminal elimination half-life was approximately 2 hours, with minimal accumulation upon repeated dosing. There were 2 primary metabolites: the major metabolite GC4520/parent GC4419 ratio was approximately 10% at all dose levels, and the minor metabolite GC4570/GC4419 ratio was <0.2% (data not shown).

Tumor outcomes

Of 46 patients, 44 were evaluable for the 1-year tumor outcome analysis (2 patients withdrew consent for follow-up; Table 5). Per study design, post-radiation therapy follow-up was completed through 12 months for all 44 patients. Three patients died during the follow-up phase: 2 patients with oropharyngeal cancer died of noncancer causes without evidence of progression, and 1 patient with oropharyngeal cancer (human papillomavirus [HPV] negative) died from locoregional and distant recurrence at 6 months. Two additional patients with oropharyngeal cancer

Table 4 Key OM efficacy parameters compared with historical controls

Severe OM (grades 3 and 4) comparison of key efficacy parameters	Comparative historical control			GC4419 phase Ib/2a		
	Unpublished data	Placebo data from phase 3 trials		Partial treatment (3 wk) (n=20)	Intermediate treatment (4-5+ wk) (n=9)	Full treatment (6-7 wk) (n=14)
		S. Sonis (n=380)	Le et al (3) (n=94)			
Incidence (%)						
Through 60 Gy	60	57	62	40	44	29
At any time	70	69	67	50	67	50
Onset (d), median (range)	≈28	35	32	>50 (25-57)	43 (15->50)	>50 (19->50)
Duration (d), median (range)	26-30	26	22	4.5 (0-77)	18 (0-68)	2.5 (0-34)

Abbreviation as in Table 1.

Results for the 14 patients receiving 30 or 90 mg for 6-7 weeks are compared with those in the initial dose escalation phase (n=20), the intermediate schedule (n=9), and representative historical controls. Patients who never developed OM of grade >2 had values of 0 days and >50 days imputed for duration and onset, respectively, of severe (grade 3-4) OM.

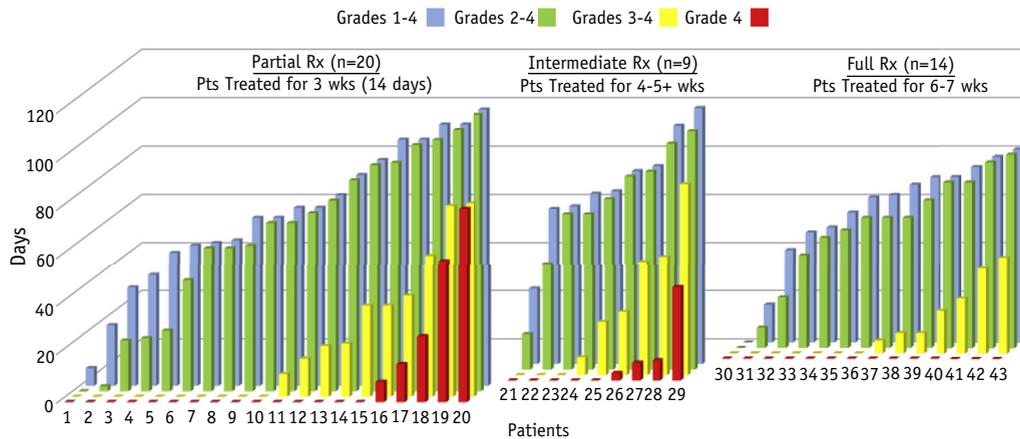


Fig. 2. Duration of all grades of oral mucositis decreased with longer GC4419 dosing. Each vertical set of bars represents oral mucositis duration by grade for an individual subject. Data are presented by the 3 dosing duration groups (14 doses/3 weeks; 4-5+ weeks; or 6-7 weeks) and arranged to increase from left to right for each subgroup for viewing clarity.

had locoregional progression at month 12 (1 HPV positive and 1 HPV unknown), and 3 patients had distant metastases at month 12. One of the 5 patients who experienced recurrence was in the full-dose cohort (90 mg × 35 doses). None of the 5 patients who experienced recurrence required cisplatin dose reduction. Two of the 5 patients received 2 full doses of cisplatin 100 mg/m² but missed the last every-3-weeks dose of cisplatin, 1 owing to patient noncompliance and 1 owing to “administrative reasons.”

Discussion

In this study we found it feasible to add the SOD mimetic GC4419 to IMRT and cisplatin. Observed safety was acceptable at all dose and duration schedules studied. Delivery of planned CRT was not compromised in the presence of GC4419. Grade 3 nausea and vomiting were more frequent at the highest dose (112 mg). Because of this, and a low threshold for additional toxicity in this patient population, GC4419 dose escalation was curtailed before reaching the study-defined MTD. The most common GC4419-associated adverse event—mild paresthesia—is similar to reports with sublingual nitroglycerine (28) and is

likely due to potentiation of nitric oxide (NO) by GC4419, as has previously been reported to occur with this class of compounds (29). Superoxide reacts rapidly with NO to remove it, and abruptly reducing the amount of superoxide present would be expected to potentiate NO’s effects.

The anticipated incidence, duration, and time to onset of severe OM in this study were favorable compared with historical controls (Table 4). These controls included the placebo arms of 2 published studies of palifermin (2, 3) and unpublished results known to one of the authors (Sonis) from control arms of multiple prospective OM studies. The unpublished historical controls are not case-matched with the present study, and stage and HPV status are not available. The unpublished experience was limited to patients with oral cavity or oropharyngeal primaries, postoperative and definitive, who received IMRT plus concurrent cisplatin (every 3 weeks or weekly). However, for all of these published and unpublished historical data, mucositis was assessed at sites receiving >50 Gy by the same OM assessment criteria (trained assessors, assessment method, assessment interval, WHO scale) as in the present trial. Although conclusions from historical, cross-study comparisons must be limited, the present results are sufficiently encouraging to warrant more rigorous assessment in a prospective controlled trial.

Oral mucositis results were best for the cohorts that received 30 or 90 mg of GC4419 for 6 to 7 weeks, consistent with expectations that GC4419 should be administered throughout the entire IMRT course to remove superoxide produced with each IMRT fraction. Patients receiving as little as 30 mg of GC4419 had little severe OM (Fig. 1). Further, OM results through 6 weeks/60 Gy are of interest because this is a common landmark expected to be reached in IMRT of all patients with locally advanced HNSCC.

Although most of our patients developed OM of WHO grade ≥2, consistent with prior reports (4), severe (WHO grade 3-4) OM is arguably more relevant to clinical benefit. Reducing severe OM should decrease the substantial day-

Table 5 Summary of tumor outcome parameters for evaluable patients (n=44)

Site	1-y LRC	1-y DM-free	1-y PFS	1-y OS
Oral cavity	7/7 (100)	6/7 (86)	6/7 (86)	7/7 (100)
Oropharyngeal	32/35 (91)	32/35 (91)	31/37 (84)	34/37 (92)
Overall	39/42 (93)	38/42 (91)	37/44 (84)	41/44 (93)

Abbreviations: DM = distant metastases; LRC = locoregional control; OS = overall survival; PFS = progression-free survival.

Values are number (percentage). Locoregional control was defined as alive without receiving alternate therapy and without locoregional progression. Two patients who died of noncancer causes were censored from the LRC and DM-free metrics, making the n=42 for those endpoints.

to-day burden of OM overall (5). As a result, increased resource usage estimated to cost approximately \$18,000 per patient (10) could be reduced. A further question is whether patients' subjective reports of mouth and throat soreness correspond to the WHO score, a relationship that held for palifermin's effects on OM in patients receiving total body irradiation/high-dose chemotherapy and hematopoietic stem cell transplant (30) but not in the trials of that drug in HNSCC patients (2, 3).

Of equal importance, IMRT treatment breaks are associated with compromised tumor outcomes in HNSCC (7, 8). That only 3 of 46 patients (6.5%) in this study had radiation therapy breaks of 5 or more consecutive fractions is promising. Treatment breaks of this duration were reported in 15% of both control and experimental patients in the 2 palifermin studies to reduce OM in HNSCC (2, 3), which used 3-field conformal radiation, and 15.1% of patients receiving IMRT/platinum and 26.9% receiving IMRT/cetuximab in the Radiation Therapy Oncology Group 0522 trial (31).

For cancer supportive care agents, a major concern is that they not compromise or antagonize the efficacy of the underlying antitumor regimen. In the present study tumor outcomes at 1 year did not seem unfavorable compared with contemporary expectations (31), but conclusions are limited owing to the small sample size and lack of a placebo arm for control.

On a mechanistic basis, GC4419 is expected not to antagonize, but instead potentially enhance, tumor radiation response. Normal and cancer cells metabolize reactive oxygen species differently. Specifically, normal cells tend to be more sensitive to elevations in superoxide anion but more tolerant of increases in hydrogen peroxide flux. They utilize redox protective enzyme systems to convert superoxide into water and molecular oxygen, removing it rapidly to prevent normal tissue damage. Although these same enzyme systems are typically active in cancer cells, moderate elevations in superoxide actually serve to promote tumor growth, but significant increases in hydrogen peroxide flux are apparently less well tolerated than for normal cells (32). Thus, therapeutic radiation, by increasing superoxide, can overwhelm the SOD enzyme system and initiate normal tissue toxicity such as OM. GC4419 can convert this excess superoxide into hydrogen peroxide, which is less toxic to normal tissue, while simultaneously maintaining or even increasing antitumor efficacy. Consistent with this are nonclinical data demonstrating synergy, especially between GC4419 and higher dose-fraction RT regimens (27), as are becoming used in stereotactic body radiation therapy.

To our knowledge this is the first clinical trial of a selective SOD mimetic to reduce radiation therapy-induced severe OM. Results in animal models of radiation OM have been reported for a manganese SOD (33), for nonselective oxygen radical scavengers (34), and for manganese porphyrins that mimic both SOD and catalase (35). None of these, however, has been tested in a clinical study of OM. A

marketed bovine-sourced copper-zinc SOD was also tested in a small study of head and neck cancer patients for treatment of radiation toxicities in head and neck cancer patients (36), but that product was subsequently withdrawn from all markets for safety reasons.

The promising OM results of this study, along with a comparative assessment of the contribution of GC4419 to the toxicity and tumor control outcomes of CRT, must be confirmed in a larger randomized, placebo-controlled setting. To that end, doses of 30 and 90 mg/d administered throughout CRT were selected for the randomized, double-blind, placebo-controlled GC4419 phase 2b trial in progress. Tumor follow-up will extend through 24 months after IMRT in that trial.

References

1. Sonis ST. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. *Oral Oncol* 2009;45:1015-1020.
2. Henke M, Alfonsi M, Foa P, et al. Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: A randomized, placebo-controlled trial. *J Clin Oncol* 2011;29:2815-2920.
3. Le QT, Kim HE, Schneider CJ, et al. Palifermin reduces severe mucositis in definitive chemoradiotherapy of locally advanced head and neck cancer: A randomized, placebo-controlled study. *J Clin Oncol* 2011;29:2808-2814.
4. Elting LS, Keefe DM, Sonis ST, et al. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: Demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. *Cancer* 2008;113:2704-2713.
5. Traynor AM, Richards GM, Hartig GK, et al. Comprehensive IMRT plus weekly cisplatin for advanced head and neck cancer: The University of Wisconsin experience. *Head Neck* 2010;32:599-606.
6. Park HS, Rutter CE, Lester-Coll NH, et al. Facility case volume and outcomes for intensity modulated radiation therapy in head and neck cancer. *Int J Radiat Oncol Biol Phys* 2016;96:E325.
7. Russo G, Haddad R, Posner M, et al. Radiation treatment breaks and ulcerative mucositis in head and neck cancer. *Oncologist* 2008;13:886-898.
8. Vera-Llonch M, Oster G, Hagiwara M, et al. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. *Cancer* 2006;106:329-336.
9. Elting LS, Cooksley CD, Chambers MS, et al. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. *Int J Radiat Oncol Biol Phys* 2007;68:1110-1120.
10. Nonzee NJ, Dandade NA, Patel U, et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis: Results from a Northwestern University Costs of Cancer Program pilot study with head and neck and nonsmall cell lung cancer patients who received care at a county hospital, a Veterans Administration hospital, or a comprehensive cancer care center. *Cancer* 2008;113:1446-1452.
11. Allison RR, Ambrad AA, Arshoun Y, et al. Multi-institutional, randomized, double-blind, placebo-controlled trial to assess the efficacy of a mucoadhesive hydrogel (MuGard) in mitigating oral mucositis symptoms in patients being treated with chemoradiation therapy for cancers of the head and neck. *Cancer* 2014;120:1433-1440.
12. Barber C, Powell R, Ellis A, et al. Comparing pain control and ability to eat and drink with standard therapy vs Gelclair: A preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis. *Support Care Cancer* 2007;15:427-440.

13. Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014;120:1453-1461.
14. Lambrecht M, Mercier C, Geussens Y, et al. The effect of a super-saturated calcium phosphate mouth rinse on the development of oral mucositis in head and neck cancer patients treated with (chemo)radiation: A single-center, randomized, prospective study of a calcium phosphate mouth rinse + standard of care versus standard of care. *Support Care Cancer* 2013;21:2663-2670.
15. Leenstra JL, Miller RC, Qin R, et al. Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: A phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). *J Clin Oncol* 2014;32:1571-1577.
16. Rao NG, Trotti A, Kim J, et al. Phase II multicenter trial of Caphosol for the reduction of mucositis in patients receiving radiation therapy for head and neck cancer. *Oral Oncol* 2014;50:765-769.
17. Sarvizadeh M, Hemati S, Meidani M, et al. Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer. *Adv Biomed Res* 2015;4:44.
18. Villa A, Sonis ST. Pharmacotherapy for the management of cancer-related oral mucositis. *Expert Opin Pharmacother* 2016;1801-1807.
19. Wong KH, Kuciejewska A, Sharabiani MT, et al. A randomised controlled trial of Caphosol mouthwash in management of radiation-induced mucositis in head and neck cancer. *Radiother Oncol* 2017;122:207-211.
20. Federal Drug Administration. Palifermin (Kepivance) Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125103s0120lbl.pdf. Accessed July 1, 2017.
21. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004;351:2590-2598.
22. Sonis S, Haddad R, Posner M, et al. Gene expression changes in peripheral blood cells provide insight into the biological mechanisms associated with regimen-related toxicities in patients being treated for head and neck cancers. *Oral Oncol* 2007;43:289-300.
23. Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer* 2004;4:277-284.
24. McCord JM, Fridovich I. Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). *J Biol Chem* 1969;244:6049-6055.
25. Thompson JS, Chu Y, Glass J, et al. The manganese superoxide dismutase mimetic, M40403, protects adult mice from lethal total body irradiation. *Free Radic Res* 2010;44:529-540.
26. Murphy CK, Fey EG, Watkins BA, et al. Efficacy of superoxide dismutase mimetic M40403 in attenuating radiation-induced oral mucositis in hamsters. *Clin Cancer Res* 2008;14:4292-4297.
27. Sishc B, Bloom D, Srinivasan K, et al. Superoxide dismutase mimetic GC4419 protects against radiation induced lung fibrosis, exhibits anti-tumor effects, and enhances radiation induced cell killing. Presented at the Radiation Research Society Annual Meeting, September 19-22, 2015, Weston, FL.
28. Physicians Total Care. NITROLINGUAL—Nitroglycerin Spray, Metered. Available at: <https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=57718>. Accessed July 1, 2017.
29. Kasten TP, Settle SL, Misko TP, et al. Potentiation of nitric oxide-mediated vascular relaxation by SC52608, a superoxide dismutase mimic. *Proc Soc Exp Biol Med* 1995;208:170-177.
30. Stiff PJ, Erder H, Bensinger WI, et al. Reliability and validity of a patient self-administered daily questionnaire to assess impact of oral mucositis (OM) on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCCT). *Bone Marrow Transplant* 2006;37:393-401.
31. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol* 2014;32:2940-2950.
32. Buettner GR, Ng CF, Wang M, et al. A new paradigm: Manganese superoxide dismutase influences the production of H₂O₂ in cells and thereby their biological state. *Free Radic Biol Med* 2006;41:1338-1350.
33. Guo H, Seixas-Silva JA Jr, Epperly MW, et al. Prevention of radiation-induced oral cavity mucositis by plasmid/liposome delivery of the human manganese superoxide dismutase (sod2) transgene. *Radiat Res* 2003;159:361-370.
34. Cotrim AP, Yoshikawa M, Sunshine AN, et al. Pharmacological protection from radiation +/- cisplatin-induced oral mucositis. *Int J Radiat Oncol Biol Phys* 2012;83:1284-1290.
35. Crapo J, Day B, Batinic-Haberle I, et al. Cancer therapy; US Pat. App. 10/051367, 2003.
36. Valencia J, Velilla C, Urpegui A, et al. The efficacy of orgotein in the treatment of acute toxicity due to radiotherapy on head and neck tumors. *Tumori* 2002;88:385-389.