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PHASE I STUDIES

Epigallocatechin-3-gallate mouthwash protects mucosa from radiation-induced mucositis in head and neck cancer patients: a prospective, non-randomised, phase 1 trial

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Summary

Radiation-induced oral mucositis has a dismal outcome with limited treatment options. We conducted a phase I study to evaluate the safety and preliminary efficacy of epigallocatechin-3-gallate (EGCG) mouthwash when given along with radiation in head and neck cancer. Patients with pathologically confirmed head and neck cancer were eligible for this study. EGCG mouthwash was administered at the assigned dosage level (starting at 440 μmol/L, three times a day) in a standard 3 + 3 dose escalation design. Mucosal toxicity, patient satisfaction, and mucositis-related pain (MTP) were assessed weekly. The primary endpoint was safety of EGCG, and the secondary endpoint was to determine the relief of the mucositis symptom. The pre- and post-treatment parameters were compared using the paired t-test. 20 patients were enrolled. The maximum tolerated dose of the EGCG mouthwash was 2200 μmol/L. Burning ($n = 1/20$) and nausea ($n = 3/20$) were the most common toxicities. No patients experienced WHO Grade 3 or higher mucositis. MTP scores significantly decreased after EGCG administration over time ($p < 0.05$). Adding EGCG mouthwash to radiotherapy is feasible without increasing toxicities. The recommended dose for phase II study is determined to be 1760 μmol/L, and EGCG administration reduces radiation-induced oral mucosal injury in patients.

Keywords Head and neck neoplasms · Epigallocatechin-3-gallate · Mucositis, radiation-induced

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Introduction

Oral mucositis is one of the main adverse events of cancer treatment [1]. Approximately 80%–100% of patients with head and neck radiation develop oral mucositis [2]. It presents as erythema and ulceration of oral mucosa, and causes pain, dysphagia, malnutrition and dysgeusia of patients. Interruption of the cancer treatment due to radiation-induced oral mucositis can lead to a decrease in cure rates, an increase in treatment costs and a reduction in quality of life [3]. Thus, oral mucositis is a highly significant, and sometimes dose-limiting, toxicity of radiotherapy. There is an urgent need for a safe and effective agent to prevent radiation-induced oral mucositis [4].

The pathogenesis of oral mucositis is extremely complex, including the amplification of the reactive oxygen species (ROS), second messengers, pro-inflammatory cytokines, and metabolic byproducts of colonizing microorganisms [5, 6]. The methods targeting these mechanisms include growth factors,

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anti-inflammatory therapies, analgesics, natural remedies, cryotherapy and laser therapies [7]. Until now these radioprotective agents have been studied in the treatment of radiation-induced oral mucositis, with conflicting results [8–10].

Epigallocatechin gallate (EGCG) is a main constituent of green tea polyphenols, which is widely used as a food preservative and safe for consumption. EGCG can alleviate beta-ray induced DNA breaks [11]. Further possible underlying mechanisms include anti-apoptosis and anti-ROS production, antibacterial and anti-inflammatory processes [12]. And our previous studies have shown EGCG as a radioprotective agent is feasible for patients with radiation-induced esophagitis and dermatitis [13–16].

The radiation response of different organs is controlled by tissue-specific factors (ie epithelial type, endocrine system, local microbial environment, and function) [17]. The response to radioprotector is similar. For example, the dilution of saliva affects the effective dose of EGCG mouthwash. We designed the phase 1 trials to assess the safety of EGCG mouthwash combined with (chemo-)radiotherapy treatment regimens in patients with head and neck cancer. Furthermore, its potential ability to reduce mucositis-related pain (MTP) was also analyzed.

Material and methods

Patients

Patients with pathologically confirmed head and neck cancer met the inclusion criteria. Other inclusion criteria were Intensity modulated radiation therapy with or without chemotherapy; ECOG performance status ≤2; adequate marrow, renal and hepatic functions; Grade I radiation-induced mucositis according to the World Health Organization (WHO) scale; the cumulative point doses to oral mucosa (right or left buccal mucosa, right or left ventral/lateral oral tongue, floor of mouth, or soft palate) of at least 60 Gy. Maximum point doses were calculated based on the dose distribution of the radiotherapy plan (Fig. 1). Patients received 66–72 Gy radiotherapy in 30–38 once-daily fractions of 1.8–2.3 Gy. Exclusion criteria included the presence of rash or unhealed wound in oral mucosa before radiation; a known allergy or hypersensitivity to green tea or EGCG. Informed consent was obtained from all patients. The study was approved by the local Institutional Review and Ethical Committees and registered at ClinicalTrials.gov (NCT01481818).

EGCG administration and maximum tolerated dose (MTD) definition

EGCG (purity ≥95% by high performance liquid chromatography) was purchased from HEP Biotech Co., Ltd. (Ningbo, Zhejiang, China) and freshly dissolved in 0.9% saline solution. The EGCG concentration escalated from 440 μmol/L, 880 μmol/L, 1320 μmol/L, 1760 μmol/L to 2200 μmol/L.[13,15] Patients gargled with 15 ml of EGCG solutions for 5 min three times per day.

The toxicity of EGCG was graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. If Grade 3 mucositis occurred, EGCG administration was discontinued and additional treatments were given at the physician's discretion. Adverse events worse than Grade 1 attributed to EGCG were considered dose-limiting toxicity (DLT), and EGCG treatment was stopped. A standard "3 + 3" phase I dose escalation design was utilized. The dose was escalated to the next level when fewer than 2 of 6 patients experienced DLT. MTD was defined as the dose level causing DLT in one-third of patients or more. The recommend dose level of EGCG was defined as the level below the level of MTD for Phase II study.

Evaluation of radiation-induced oral mucositis

All patients were assessed using WHO, Patient satisfaction tool (PST), the Oral Mucositis Assessment Scale (OMAS) and Numerical Rating Scale (NRS) weekly. WHO mucositis score was as followed: 0 = none; 1 = soreness and erythema; 2 = erythema, ulcer, patient could swallow solid diet; 3 = ulceration, extensive erythema, patient could not swallow solid food; 4 = mucositis to the extent that alimentation was not possible. OMAS ulceration score (total OMAS scores of ulceration/number of sites with ulceration) was as followed: Grade 0 = no lesion; Grade 1 = <1 cm^2; Grade 2 = 1–3 cm^2; Grade 3 = >3 cm [18]. PST evaluation criteria included mouth and throat pain, swallowing situation, eating and overall symptom, as described in Ref. 19. Moreover, MTP was measured by NRS (patient reporting scale of 0–10) [15]. The assessments continued until 2 weeks after the end of radiotherapy.

Statistical analysis

SPSS (version 17.0; SPSS Inc., Chicago, IL) was used for statistical analysis. The differences in the score before, during and after treatment were analyzed using a paired t-test. A value of $P < 0.05$ was adopted as the level of statistical significance.

Results

Patients

The study was opened on October 3th 2013 and the last patient was enrolled on November 21th 2014. Four patients discontinued EGCG based on their preferences, 3 patients

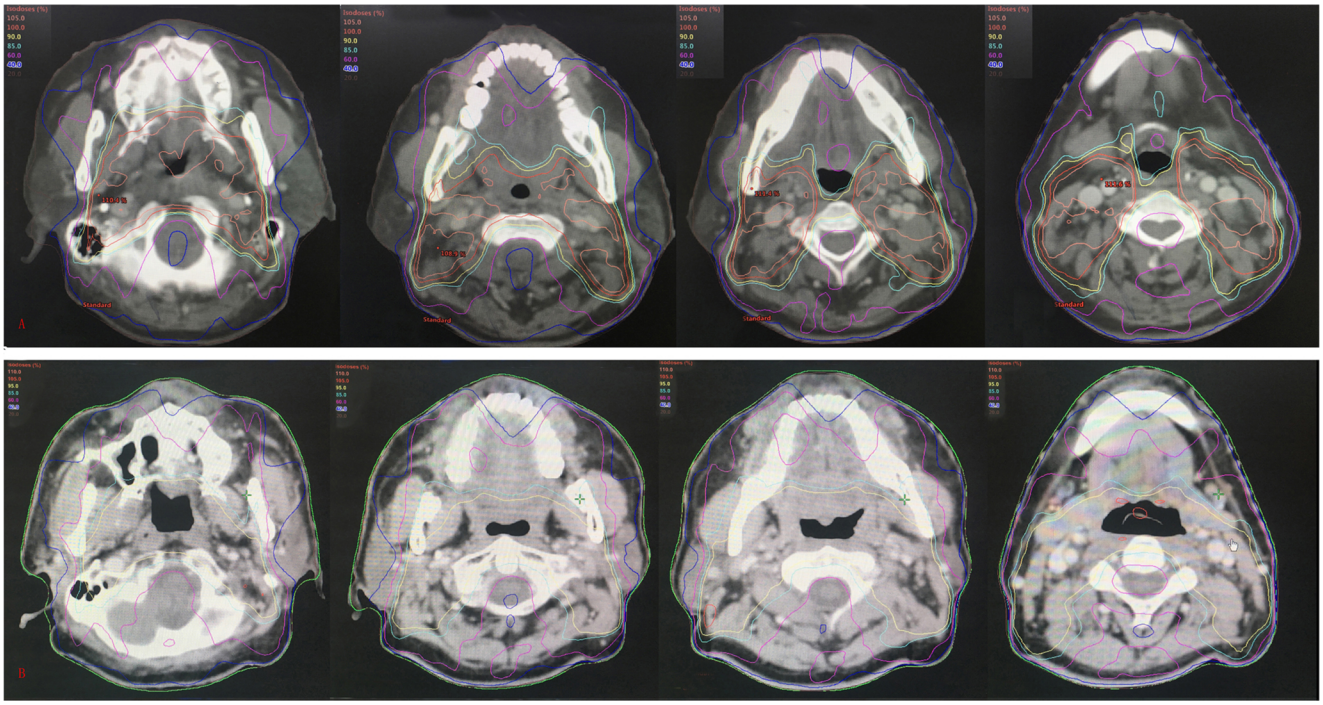

Fig. 1 Dose distribution of an intensity-modulated radiation therapy plan for the patients with head and neck cancer shows the dose gradient across the oral cavity in four different level. A: patient No.13 with nasopharyngeal cancer; B: patient No.3 with hypopharyngeal cancer

underwent late-course hypofractionated radiotherapy (2.5-3Gy/f) and 2 patients received surgery. Finally, 20 patients completed the course of therapy per study protocol. The demographic, clinical and treatment characteristics of patients were shown in Tables 1 and 2. Of the 20 patients, 2 (10%) had diabetes. Twelve patients developed Grade 1 radiation mucositis in the second week after the beginning of radiotherapy and the rest in the third week. And the median total duration of EGCG was 7 weeks.

Safety and effectiveness

All patients were treated with radiotherapy in an uninterrupted course (a median dose of 70Gy). All patients received chemotherapy doses as planned, except for two who required a 75% dose reduction due to Grade 2 neutropenia. Grade 2 burning-feeling and Grade 1 nausea in one patient and Grade 2 nausea in the other two patients were happened in 5 min after EGCG application, and they were considered to have a possible relationship with EGCG application. None of the other reported toxicities considered as possibly, probably, or definitely related to EGCG were observed. Therefore, DLT was Grade 2 burning and nausea. A DLT of Grade 2 nausea was observed in one patient at dose Level 2 (EGCG 880 μmol/L) after 4 weeks of administration. Three additional patients enrolled at this dose level did not experienced toxicities of EGCG again. Since 2 of 5 patients experienced DLT at dose Level 5 (1 and 3 weeks after EGCG treatment was initiated), the MTD of EGCG was 2200 μmol/L. And the 1760 μmol/L was defined as the starting dose for the phase II trial.

17/20 (85%) patients were evaluable for efficacy analysis. Due to the toxicity, the other 3 patients with EGCG treatment interruption were excluded. Of the 17 patients, the maximum oral mucositis score was grade 1 in 7 patients and grade 2 in the other 10 patients during treatment. In the weekly assessment, less than 50% patients had Grade 2 mucositis, the highest level of mucosal toxicity in the study. Figure 2 showed the changes in the proportion of patients with Grade 2 mucositis (WHO), ≥Grade 1 ulceration (OMAS) and Grade 2 ulceration (OMAS) with the prolongation of EGCG treatment time. The scores did not deteriorate in most patients during the first 4 weeks after EGCG treatment, although the total dose of radiotherapy continued to accumulate. And more than half of the patients improved their symptoms according to PST criteria in the latter stage (Fig. 3). MTP scores at various post-treatment time points were significantly lower than before EGCG application (Table 3). Even if patients were given different doses of EGCG and continued to receive radiotherapy, MTP score at the end of radiotherapy was significantly lower than at the time of enrollment according to NRS. After the end of radiotherapy, continuous application of EGCG further reduced the patient's pain score.

Tumor outcomes

The response of the tumor to RT at the end of radiotherapy was as follows: partial response in 17 (PR,

Table 1 Patient demographics and disease characteristics

Variable	No. of patients ($N = 24$)	%
Age(years)		
Median	51	
Range	21–70	
Smoking status (current or within 6 months)		
Yes	7	35
No	13	65
Primary tumor location		
Nasopharynx	12	60
Hypopharynx	8	40
Histology		
Squamous cell carcinoma	11	55
Squamous cell carcinoma variant	9	45
Performance status (ECOG)		
0	8	40
1	12	60
T stage		
T1	0	0
T2	5	25
T3	7	35
T4	8	40
N stage		
N1	3	15
N2	16	80
N3	1	5
AJCC stage		
III	8	40
IVA	11	55
IVB	1	5
Chemotherapy		
No	11	55
Yes	9	45

85%) and stable disease in 3 (SD, 15%). After a median follow-up of 52 months (range, 6–68 months), estimated 1-, 2-, and 4-year overall survival (OS) rates were 90%, 85%, and 65%, respectively.

Discussion

In this study, we find it feasible to add EGCG solution to radiotherapy. EGCG mouthwash has an acceptable safety profile. None of ≥Grade 3 toxicities are considered related to EGCG. DLTs are CTCAE Grade 2 burning and nausea. The MTD is defined as 2200 μmol/L. The next lower dose level (1760 μmol/L) below the MTD is the recommended dose for phase II studies. It was significantly higher than the dose level in an oral or topical formulation [13–16]. The main reason may be saliva secretion in response to taste stimuli of EGCG mouthwash, and the concentration of EGCG is diluted by the increased volume of saliva.

Radiotherapy-induced oral mucositis develops over several weeks, with a relatively late appearance of clinically detectable severe Grade 3–4 toxicity. There is typically a high incidence of persistent severe mucositis after the patient received a cumulative radiotherapy of 5000 cGy. In the study, no patients experience WHO Grade 3 or higher mucositis, feeding tube placement or liquid diet throughout EGCG application. Despite lack of the exact binomial distribution test, the rate of Grade 3–4 toxicity in the study is markedly lower than the historical rate (6%–45%) [20, 21]. From the 5th week of EGCG treatment, more than 50% of patients report improvement in symptoms according to PST. In order to directly demonstrate its efficacy, this study is

Table 2 EGCG treatment and radiation dermatitis scoring

	Radiation dose as EGCG treatment	Radiation total dose	EGCG dose (μmol/L)	WHO / OMAS score									
				baseline	The week after EGCG application								1 week after the end of radiation	2 weeks after the end of radiation
					1	2	3	4	5	6	7	8		
1	26Gy/13f	66Gy/33f	440	1/1	1/1	1/0	2/2	2/2	1/0	1/0	N	N	1/0	1/0
2	18Gy/10f	67.4Gy/35f	440	1/1	1/1	1/1	1/1	1/1	1/0	1/0	1/0	N	1/0	1/0
3	23.4Gy/13f	66.4Gy/36f	440	1/1	1/0	1/1	2/2	1/1	1/0	1/0	0/0	N	1/0	0/0
4	24Gy/12f	70 Gy/35f	880	1/0	1/1	2/1	2/2	2/2	1/1	1/1	0/0	N	1/1	0/0
5	20Gy/10f	70Gy/35f	880	1/0	1/0	1/0	1/1	–	–	–			–	–
6	16.2Gy/9f	68.4Gy/38f	880	1/0	2/1	1/0	1/0	1/0	1/0	1/0	1/0	0/0	1/0	0/0
7	18Gy/9f	72Gy/36f	880	1/1	1/1	1/1	1/1	1/1	1/1	2/2	1/1	N	2/2	1/1
8	30Gy/15f	66Gy/33f	880	1/1	2/1	2/1	2/1	1/1	1/1	N	N	N	1/1	1/1
9	20Gy/10f	70Gy/35f	880	1/1	2/1	2/1	2/2	2/2	2/2	1/1	1/1	N	1/1	1/1
10	12Gy/6f	72Gy/36f	1320	1/0	1/1	2/1	1/1	1/1	1/1	1/1	2/2	1/0	2/2	1/0
11	14.4Gy/8f	68.4Gy/38f	1320	1/0	1/1	1/1	1/1	1/1	1/1	1/1	1/0	0/0	1/0	0/0
12	30Gy/15f	68Gy/34f	1320	1/1	2/2	1/1	1/1	1/0	0/0	N	N	N	1/0	0/0
13	28Gy/14f	70Gy/35f	1760	1/1	1/1	1/0	1/1	2/2	1/0	1/1	1/1	N	1/1	1/1
14	18Gy/9f	70Gy/35f	1760	1/0	2/0	1/0	1/0	1/0	1/0	1/1	1/0	0/0	1/0	0/0
15	30Gy/15f	72Gy/36f	1760	1/1	1/1	1/1	2/2	2/2	2/2	1/1	1/1	N	1/1	1/1
16	16Gy/8f	70Gy/35f	2200	1/0	1/0	–	–	–	–	–			–	–
17	14Gy/7f	66Gy/33f	2200	1/0	1/1	1/1	1/1	–	–	–			–	–
18	16Gy/8f	70Gy/35f	2200	1/0	1/0	1/0	1/0	1/0	1/1	1/0	1/0	N	1/0	1/0
19	19.8Gy/11f	66Gy/35f	2200	1/1	1/1	2/1	2/1	2/1	2/1	1/1	1/0	N	1/1	1/0
20	20Gy/10f	72Gy/36f	2200	1/0	1/0	1/0	2/2	2/2	1/1	1/1	1/1	0/0	1/1	0/0

EGCG: Epigallocatechin-3-gallate; WHO score: World Health Organization (WHO) score; OMAS score: Oral Mucosal Assessment Scale score;-: the data were not be recorded because the patients experienced dose-limit toxicity and discontinued EGCG treatment; N: EGCG treatment ended

designed to give participants EGCG mouthwash after the occurrence of grade 1 mucositis. The results show that it can decrease the MTP score despite continuation of radiotherapy. The short-term efficacy of cancer treatment and OS of patients in the study is similar to previous studies [20, 21]. These may indirectly prove that EGCG had no protective effect on tumors during radiotherapy. Although the reliability of conclusions from historical comparisons must be limited, the current results are encouraging enough to warrant more rigorous assessment in a randomized controlled study.

The bottleneck created by normal tissue radiation damage is a strong motivation to develop radioprotectors. The systematic review studies have generated mostly inadequate and/or conflicting results for use of oral care products in preventing or treating radiation damage. Recent researches suggest that low-level laser therapy offer the most consistent benefits for patients with oral mucositis relative to no interventions. But barriers to the acceptance of low-level laser therapy treatment contain the variable quality of these studies, the wide variation in laser parameters, the cost of laser appliance and no access to deeper area at risk of mucositis [10]. There remains a need to continue investigating new products and novel approaches

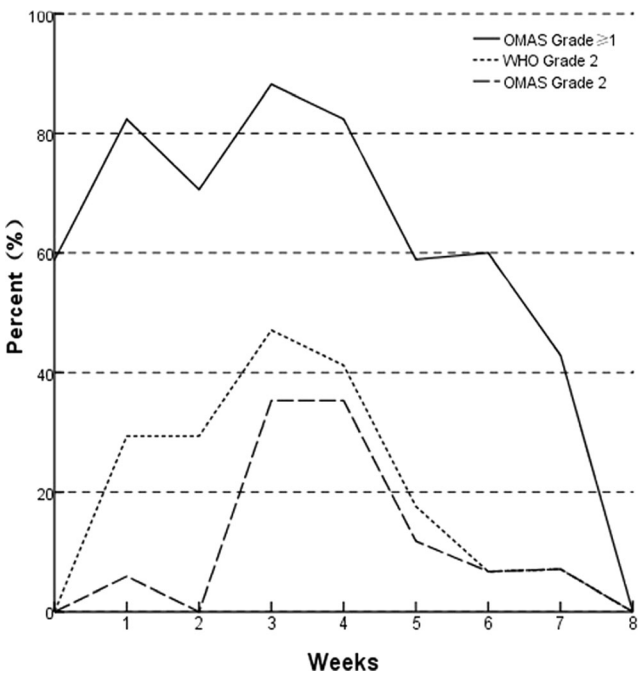

Fig. 2 Percentage change of OMAS Grade ≥ 1, OMAS Grade 2 and WHO Grade 2 during EGCG treatment. X-axis: the time point of the first to eighth week after EGCG prescription. Y-axis: the percentage in each week

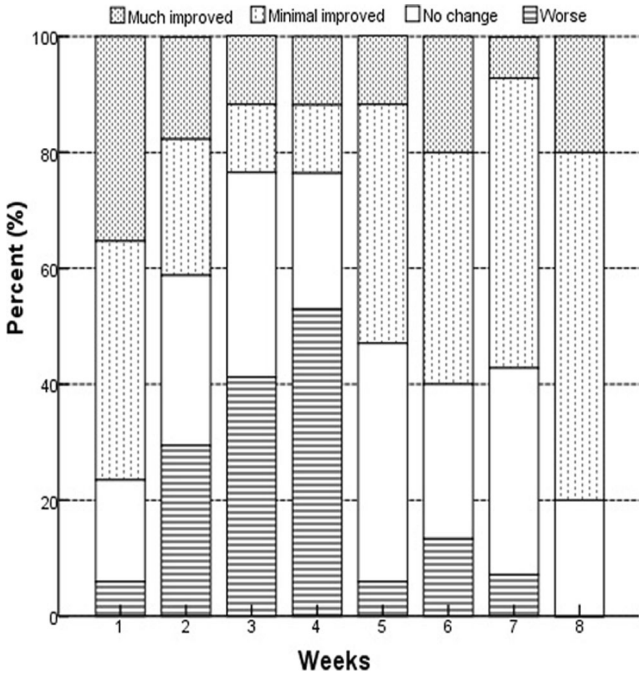

Fig. 3 Overall results of PST. Improvement of symptoms was observed in head and neck cancer patients with time after EGCG treatment, especially in the late course. X-axis: the time point of the first to eighth week after EGCG prescription

for minimizing radiation oral mucositis. EGCG enables not only to protect normal cells, but also to improve tumor radiosensitivity [22, 23]. It is worth exploring that EGCG with these differential effects is applied to cancer radiotherapy [24].

EGCG has the capacity to defend radiation-induced damage nearly in whole process of oral mucositis. Radiation induced oral mucositis is initiated by direct injury to basal epithelial cells. DNA-strand breaks can result in cell death or injury. And non-DNA injury is formed by a variety of mechanisms, including the generation of ROS, damage response by the activation of nuclear factor-κ B (NF-κB)/ NF-E2-related factor 2 (Nrf2) and further tissue injury caused by tumor-necrosis factor-α (TNF-α) and interleukin 6 (IL-6). The above signaling molecules also form a positive-feedback loop, which amplify the original effects of radiotherapy. Therefore, the epithelium starts to thin and patients begin to develop mucositis [25]. Correspondingly, the effects of EGCG against radiation damage are as follows: First, it can protect DNA-strand breaks by directly intercalating with DNA [26]. Secondly, it significantly decreases ROS generation by trapping the free radicals [22]. Thirdly, it not only upregulates expression of Nrf2-controlled antioxidant genes, but also reduces NF-κB activation by inhibiting AKT signaling pathway and activating AMPK signaling pathway [27]. Finally, it also can inhibit irradiation-induced cytokine production including TNF and IL-6 via the suppression of c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase activity [28, 29].

The current study has its own limitations. It is a single-center study, and involves widely heterogeneous patients treated either with or without concurrent chemotherapy using different concentrations of EGCG. The study is non-controlled and hence, needs confirmation in a randomized controlled setting, which has already begun with a similar population at our center.

Conclusions

In conclusion, the recommended dose of EGCG mouthwash is 1760 μmol/L. EGCG mouthwash is well

Table 3 The compares among MTP score at various time points

Paired t-test	N	Score (mean ± SD)	P
Baseline vs the 1th week after EGCG	17	3.59 ± 1.06 vs 2.59 ± 1.23	t = 3.12, $p = 0.007$
Baseline vs the 2th week after EGCG	17	3.59 ± 1.06 vs 2.35 ± 1.32	t = 2.97, $p = 0.009$
Baseline vs the 3th week after EGCG	17	3.59 ± 1.06 vs 2.59 ± 1.23	t = 2.24, $p = 0.039$
Baseline vs the 4th week after EGCG	17	3.59 ± 1.06 vs 2.85 ± 1.19	t = 2.13, $p = 0.049$
Baseline vs the 5th week after EGCG	17	3.59 ± 1.06 vs 2.18 ± 1.24	t = 3.43, $p = 0.003$
Baseline vs the 6th week after EGCG	15	3.59 ± 1.06 vs 1.87 ± 0.74	t = 4.80, $p < 0.001$
Baseline vs the 7th week after EGCG	14	3.59 ± 1.06 vs 1.29 ± 0.99	t = 4.70, $p < 0.001$
Baseline vs the 8th week after EGCG	5	3.59 ± 1.06 vs 0.60 ± 0.55	t = 2.75, $p = 0.051$
Baseline vs at the end of radiotherapy	17	3.59 ± 1.06 vs 2.24 ± 1.09	t = 3.83, $p = 0.001$
Baseline vs the 1th week after the end of radiation	17	3.59 ± 1.06 vs 1.94 ± 0.90	t = 4.67, $p < 0.001$
Baseline vs the 2th week after the end of radiation	17	3.59 ± 1.06 vs 0.82 ± 0.64	t = 9.11, $p < 0.001$

tolerated and significantly reduces the pain. This result suggests potential benefits on improving the oral mucositis in patients with head and neck radiation and justifies a Phase II trial.

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Compliance with ethical standards

Conflict of interest WZ declares that he has no conflict of interest. HM declares that he has no conflict of interest. LJ declares that he has no conflict of interest. HZ declares that he has no conflict of interest. XL declares that he has no conflict of interest. XM declares that he has no conflict of interest. XZ declares that he has no conflict of interest. LX declares that he has no conflict of interest. JY declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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