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Phase I trial

A phase I study of concurrent chemotherapy and thoracic radiotherapy with oral epigallocatechin-3-gallate protection in patients with locally advanced stage III non-small-cell lung cancer

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ABSTRACT

Background and purpose: Patients with unresectable stage III non-small-cell lung cancer receiving concurrent chemoradiotherapy often develop esophagitis that may lead to unplanned treatment interruptions, which may severely reduce rates of locoregional tumor control and survival. No effective treatment that would reduce the incidence and severity of this complication has been identified up to now. Although acceleration of normal tissue protection using epigallocatechin-3-gallate (EGCG) has been reported, its actual clinical practicability remains obscure.

Methods and materials: This is a phase I study of EGCG in combination with standard chemoradiation in surgically unresectable stage III non-small-cell lung cancer. Chemotherapy (cisplatin and etoposide) was given concurrently with radiation. EGCG solution was swallowed three times a day after the occurrence of grade 2 esophagitis at six concentration levels and dose escalation followed a standard phase I design. Esophageal toxicity and patient-reported pain was recorded weekly.

Results: Twenty-four patients with AJCC stage IIIA (six) and IIIB (eighteen) completed the course of therapy. Twelve had squamous histology, ten adenocarcinoma, and two not specified. Patients were treated in six cohorts at six dose levels of EGCG. RT was not interrupted with a median dose of 64 Gy. There were no dose-limiting toxicities reported in all EGCG dosing tiers. Dramatic regression of esophagitis to grade 0/1 was observed in 22 of 24 patients, whereas grade 2 esophagitis persisted in 2 of 24 patients at the end of radiotherapy. The pain score was also reduced from a mean of 4.58 ($N = 24$), 1.29 ($N = 24$), 1.42 ($N = 24$), 0.96 ($N = 23$) to 1.13 ($N = 16$) every week in turn.

Conclusion: We conclude that the oral administration of EGCG is feasible, safe and effective. The phase II recommended concentration is 440 μmol/L.

Lung cancer is the leading cause of cancer-related deaths among both men and women [1]. More than 33% of patients diagnosed with non-small-cell lung cancer (NSCLC) present with stage III, and recent clinical trials have established the efficacy of concurrent chemoradiotherapy (CRT) [2]. However, complications such as acute radiation-induced esophagitis (ARIE) may cause significant morbidity, unplanned treatment interruptions, and a decreased chance of getting an effective dose. These issues may reduce tumor control and survival rates, as well as the Patients' quality of life (QOL) [3].

Green tea extracts have been shown to have various health benefits due to their strong anti-inflammatory and anti-oxidant activities [4–6]. In different animal systems they protect normal epithelial cell from carcinogens, by inducing growth arrest, antiangiogenic properties, effects on folate metabolism, effects on DNA damage, inhibition of telomerase, proteasome inhibition or apoptosis and finally cell death [7,8]. Epigallocatechin-3-gallate (EGCG) constitutes about 55–70% of total polyphenols in tea extracts present as the most abundant compound. It was believed that EGCG posses scavenging activity for superoxide anion, hydroxyl radical and hydrogen peroxide. Although EGCG has been demonstrated to inhibit the hydrogen peroxide (H_2O_2) radical induced oxidative damage to DNA, there are few reports of its radioprotective potential [9]. An experiment shows that the protective effect of EGCG on puC18 plasmid DNA scission against β and γ-radiation is attributable to its H_2O_2 radical scavenging ability as well as its

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intercalation with DNA [10]. Richi et al. have shown protective effect of EGCG against γ-radiation induced mortality and cell death of normal cells in vitro [6]. Moreover, oral administration of EGCG to irradiated mice, significantly counteracted radiation-induced changes in hematological parameters, small intestine and submandibular glands [11–13].

The protection of normal tissue during radiotherapy has been a strong motivation for development of exogenous radioprotectors and many studies have also proposed that EGCG could sensitize cancer cells to radiation [14]. However, not much work has been done on the radioprotective aspect of EGCG in clinical trial and its potential use as a radio-protecting agent in radiation/chemoradiotherapy. Therefore, we conducted this phase I study of EGCG therapy protection of the esophagus from damage induced by chemoradiotherapy. For concurrent chemotherapy, we used a combination of cisplatin and etoposide.

Material and methods

This study was approved by the local study review and ethics board, whose registration number is NCT01481818 (clinicaltrials.gov). Informed consent was obtained from all patients.

Patients

Patients were eligible if they had pathologically documented NSCLC. Patients were required to have the seventh edition of American Joint Committee on Cancer (AJCC) stage IIIA and were considered medically inoperable, or stage IIIB. Eligible patients were also required to have met the following criteria: age $\geqslant$18 years; ECOG PS 0–1; no prior systemic chemotherapy or radiation to the thorax; adequate hematologic (granulocytes $\geqslant$2000/ml, platelets $\geqslant$100,000/ml, hemoglobin >8 gm/dl), hepatic function (bilirubin <1.5 normal), and renal values (creatinine clearance >50 ml/min); FEV1 >800 cc; The exclusion criteria were as follows: pregnancy or lactation; a known allergy or hypersensitivity to EGCG; patients with mediastinal tumor or metastatic lymph nodes which invade esophagus; the percentages of esophagus volume receiving above 50 Gy (V50) <30%.

Study design and treatment

This is a phase I study to assess the safety and effectiveness of EGCG in combination with etoposide, cisplatin, and thoracic radiotherapy. Chemotherapy was identical to that given in the previous trial [2]: cisplatin, 50 mg/m^2/d on days 1, 8, 29, and 36; etoposide, 50 mg/m^2/d on days 1–5 and 29–33; and RT (all received three dimensional conformal radiation), 1.8–2.0 Gy per day, 5 days a week, starting within 24 h of the first day of chemotherapy. A protocol-mandated hydration and polyantiemetic regimen was used for all patients. Weekly complete blood counts with a differential and a chemistry battery before each chemotherapy cycle were required.

All the patients underwent 3D-conformal radiotherapy. Vacuum bags were used to improve reproducibility during daily treatments. 3 mm thick CT scan slices were obtained and then directly transmitted to the Eclipse treatment planning system® (Eclipse 8.6, Varian Medical Systems). RT treatment planning was based on recent chest computed tomography scans. Gross tumor volume (GTV) encompassed primary mass and metastatic regional lymph nodes observed on CT scans. Planning target volume included GTV and 0.5–1.5 cm margins for lymph nodes, 1.0–2.0 cm for primary tumor. Dose distribution was calculated with tissue heterogeneity correction. The total dose was planned at 60–66 Gy in 30–33 fractions over 6–7 weeks. The radiation dose was prescribed to the isocenter with minimum target dose of 95% and maximum dose of 107% covering 95% of PTV. For the purpose of consistency the critical normal tissues was recontoured in all cases by a single radiation oncologist. The entire esophagus was contoured from the border of the cricoid cartilage to the gastroesophageal junction. The dose constraints were: mean esophagus dose <34 Gy, mean lung dose (containing the primary tumor) 25 Gy, the maximum spinal cord $\leqslant$50 Gy, total heart $\leqslant$35 Gy.

The treatment with the EGCG solution was given to 24 patients undergoing chest CRT immediately after the documentation of grade 2 dysphagia which significantly influenced quality of life as the lowest toxicity [15]. EGCG is given 2 h (2 h) before the daily radiation whose half-life is around 3 h [16]. Studies on EGCG (purity $\geqslant$95% by HPLC; from NINGBO HEP Biotech Co., Ltd.) use various concentrations dissolved in 0.9% saline solution three times a day [14]. A new batch is made up each time. For esophageal application, repeated swallowing of 10 ml of the EGCG solution is indispensable to assure the prolonged presence of drug the esophageal walls. We have chosen a dose of 40 μmol/L as the lower limit for this phase I study by referring to previous studies. Six dose levels for EGCG were defined as following: 40, 80, 140, 210, 300, and 440 μmol/L per dose. Dose escalation proceeded according to a standard phase I design with three patients initially treated on each tier. If, on any dose tier of EGCG, two of three patients or two of six patients experienced a grade III or IV toxicity due to EGCG, dose escalation of EGCG would cease. The maximally tolerated dose (MTD) was defined as the highest dose with fewer than one-third of patients experiencing a dose-limiting toxicity (DLT) due to EGCG. All patients on a tier were required to be observed for 8 weeks after starting treatment before the dose of EGCG was escalated. Immediately after the documentation of grade 2 dysphagia, the EGCG solution was given during radiotherapy and for additional two weeks after radiotherapy was completed. Steroids, non-steroidal anti-inflammatory drugs, narcotics, local anesthetics, or other antibiotic/antifungal therapy were not given unless esophagitis progressed to grade 4. RT was not interrupted unless persistent or deteriorating dysphagia was present after therapy. In cases that were unresponsive to therapy, RT was interrupted, and patients were supported with methylprednisolone, analgesics, antifungal therapy, or intravenous fluid administration as appropriate until recovery. Nasogastric tubes were to be used only in unresponsive patients whose grade 4 toxicity persisted for more than 3 days after toxicity documentation.

Statistical methods

The primary purpose was to evaluate safety and to determine the phase II recommended dose of EGCG. A standard phase I design was implemented. The study planned to treat three patients each at six tiers. If no DLTs (grade III/IVtoxicity due to EGCG) were observed, the dose of EGCG would be escalated to the next tier. If one DLT was observed, the cohort would be expanded to six patients. If two of six patients experienced a DLT, dose escalation would cease and the next lowest dose would be declared to be the MTD. If none of three or one of six patients experienced DLT at the 440 μmol/L tier, that dose would be defined as the starting dose for phase II and the MTD would be undefined. The secondary objective for this phase I trial was to demonstrate the effectiveness of EGCG preliminarily. Esophageal toxicity was recorded weekly using a grading scale based on symptomatology, following the Radiation Therapy Oncology Group (RTOG) scoring system (Supplementary Table S1). Patient-reported pain related to esophagitis was measured using the numerical rating scale (NRS) every week from EGCG application to 2 weeks after the end of radiotherapy. The differences in symptom score before, during and after treatment were tested using paired *t*-test. The chi-square test is used to examine differences with categorical variables. SPSS (version 17.0; SPSS Inc., Chicago, IL) was used for statistical

analysis. All statistical tests were conducted at a two-sided level of significance of 0.05.

Result

The study was activated on September 2011, and closed on December 2012, after 29 consecutive patients were accrued. Five of the 29 patients did not meet other eligibility criteria (such as only experienced acute esophagitis with RTOG Grade 1) and were excluded from the primary analysis. Characteristics of the twenty-four fully eligible patients are listed in Table 1.

24 patients completed the course of therapy per study protocol and were treated in six cohorts at six dose levels of EGCG: 40 (three patients), 80 (three patients), 140 (three patients), 210 (three patients), 300 (six patients), and 440 μmol/L (six patients). Esophageal mean doses on each dose of EGCG: 29.70 ± 2.69; 29.10 ± 4.28; 28.60 ± 2.33; 30.07 ± 4.74; 28.50 ± 3.04; 28.67 ± 3.15; 28.98 ± 3.02, $p = 0.982$. Five patients required one reduction of the chemotherapy doses by 75% secondary to grade 2 neutropenia. RT was delivered without treatment breaks to all 24 patients, and the median dose of radiation was 64 Gy. This early radiation toxicity appeared in 1 of 24 patients during the second week, 15 of 24 patients during the third week, in 7 of 24 patients during the fourth week, and in all 24 patients during the fifth week. And the mean duration of EGCG treating time is 34.8 days (15–58 days).

Overall response rate for the standard chemoradiation regimen was 66.7%, which was measured by CT scan 6–8 weeks after completion of treatment. Complete response (CR) was obtained in 0 patients, partial response (PR) in sixteen, stable disease (SD) in three, and progression (PD) in five. The EGCG solution was generally well tolerated, with most of patients complaining of its very nauseating taste. Consumption adverse events reported during the treatment are summarized in Table 2. Grade 2 excess gas and a grade 1 upset stomach in one patient and grade 2 heartburn in another patient were considered to have a possible relationship to EGCG. None of the other reported toxicities were considered possibly, probably, or definitely related to EGCG. There were no DLTs reported in all six dosing tiers. The 440 μmol/L dose was defined as the starting dose for the phase II trial.

Although RT was not interrupted, a significant, impressive relief was reported even within 24 h. Fig. 1 shows the rate of resolution of esophagitis during therapy period. Dramatic regression of esophagitis to grade 0/1 was observed in 22 of 24 patients, whereas grade 2 esophagitis persisted in 2 of 24 patients at the end of radiotherapy. Progression of dysphagia to severe grade 3, requiring hospitalization and intravenous fluid administration, was not seen in these patients. However, the rapidly relief of grade 1/2 esophagitis within 2 weeks of EGCG treatment after radiotherapy was observed in all patients, which points out the need for treatment continuation. The regression of esophagitis did not seem to depend on the onset time of EGCG. The similar result was also observed in the patient-reported pain related to esophagitis. The score was also reduced from a mean of 4.58 ($N = 24$), 1.29 ($N = 24$), 1.42 ($N = 24$), 0.96 ($N = 23$) to 1.13 ($N = 16$) every week in turn. And the mean score of all patients at the end of radiotherapy was only 1.13 ($N = 24$). The pain scores not only between onset and after first week application, but also between the second and third week on the NRS diary were statistically different, even during the different EGCG dose period. The most important is that the difference was also observed between the onset and the end of radiotherapy (Table 3).

Table 1
Patient demographics and clinical characteristics.

Variable	No. of patients ($N = 24$)	%
Age (years)		
Median	57	
Range	37–72	
Sex		
Male	20	83.3
Female	4	16.7
Smoking status		
Yes	15	62.5
No	9	37.5
Performance status (ECOG)		
0	10	41.7
1	14	58.3
AJCC stage		
IIIA	6	25
IIIB	18	75
Histology		
Squamous	12	50.0
Adenocarcinoma	10	41.7
Poorly differentiated	2	8.3
Radiotherapy dose (Gy)		
Median	64	
Range	60–66	
Esophagus V50		
Median	37	
Range	47–31	
Mean esophagus dose		
Median	28.9	
Range	24.6–34.0	

Table 2
Acute toxic effects.

Adverse events	Grade 1/2 (No. of patients)	Grade 3/4 (No. of patients)
Hematologic		
Neutropenia	10	3
Anemia	10	2
Thrombocytopenia	8	1
Infection	2	1
Nonhematologic		
Esophagitis	24	0
Nausea/vomiting	17	3
GI toxicity	5	2
Kidney	3	0
Lung fibrosis	12	0
Respiratory	3	0
Cardiovascular	2	0
Neurologic	10	0
Skin	19	0
Allergy	2	0
Other	8	4

Discussion

ARIE is a major dose dependent side effect in CRT for locally advanced NSCLC [17]. There are two main approaches to the prevention of ARIE: one is avoiding esophageal radiation by optimized treatment planning, dose distribution and radiation-fractionation techniques, and the other is the delivery of radiation protective chemical/biological agents. There is little heterogeneity with regard to continual improvement in treatment planning and techniques for decreasing toxicity. More recently, 3DCT planning has enabled investigators to assess the relationship between esophageal dose–volume histogram (DVH) parameters and clinically significant ARIE. The most complete information relating DVH parameters to actual and modeled rates of esophagitis are in relation with the parameters of mean esophagus dose, V35, V50 and V60 Gy (percentage volume of esophagus receiving a specific dose

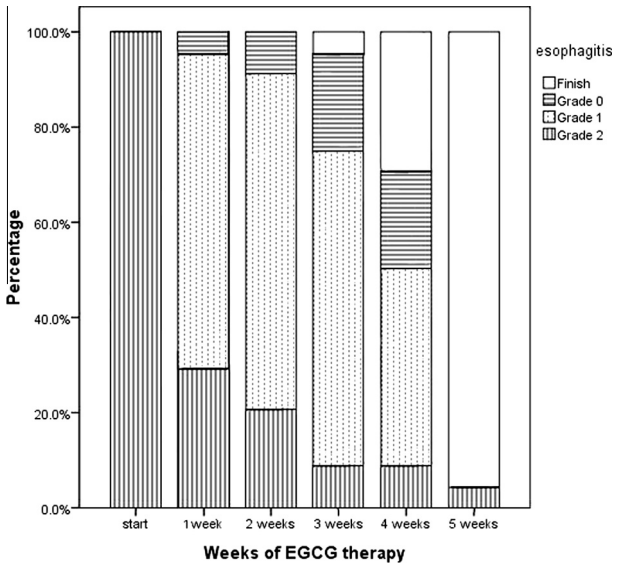

Fig. 1. Improvement of grade 2 esophagitis observed in 24 lung cancer patients undergoing RT after the treatment of EGCG.

Table 3
Patient-reported pain during EGCG treatment.

Pair	No. of patients	Pain paired differences		
		Mean	SD	*P*
V1–V2	24	3.29167	1.33447	<0.001
V2–V3	24	−0.12500	1.29590	0.641
V3–V4	23	0.39130	0.83878	0.036
V4–V5	16	−0.06250	1.18145	0.835
V5–V6	1			
V1–V_{End}	24	3.45833	1.61458	<0.001

V1–6: pain related to esophagitis was measured using the NRS from the first to the sixth times; V_{End}: pain at the end of radiotherapy.

in 35, 50 and 60 Gy). Minimizing these parameters while still delivering lethal doses to cancer has provided benefits in decreasing treatment-related toxicity [17–20]. With the occurrence of various novel technologies such as 4DCT, gating, intensity-modulated radiation therapy and image-guided radiation therapy, continued investigation in decreasing normal tissue toxicity is critically going forward. Radioprotective agents, including sulfhydryl compounds such as amifostine, nitroxides, antioxidant compounds such as glutathione, and non-antioxidant radioprotectors such as hormone melatonin, have been tried intraorally or intravenously with some success [21–22]. However, evidence of efficacy, lack of tumor protection, and acceptable toxicity are all important considerations for developing these agents. Although amifostine remains the only agent currently in clinical use as a radioprotector, more consistent reporting of long term toxicity is needed [23]. A number of other candidate compounds such as EGCG, will be tested in future years as a way to reduce radiation-induced normal tissue toxicity and complications.

The use of EGCG has been shown to be associated with cancer prevention and treatment in vitro and in animal models, not only through additive or synergistic effects but also through amelioration of deleterious side effects, in a high variety of cancer types including skin, breast, prostate, colorectal, liver and lung cancer [24]. It is known that DNA, other constituents of the cell (such as membrane, lipid, and cellular protein) and antioxidant enzymes all get affected resulting in cellular mortality [25]. ARIE has been associated with the use of radiotherapy, aexacerbated by chemotherapy [26]. The primary radiation damage is due to the aqueous free radicals after the radiolysis of water. They act as molecular marauders and in turn damage DNA which is considered to be primary target [27]. EGCG has the capacity to protect DNA against radiation-induced damage under both acellular and cellular conditions, either by directly intercalating with DNA, by trapping the free radicals or by repair of the damage produced by free radicals. A new study has demonstrated the protection against radiation induced damage both DNA as well as other components of the cellular systems membranes and antioxidant enzymes in normal splenocytes [6]. Although EGCG exerted protection to radiation treated normal cells, it has been reported to kill cancerous cells due to its oxidant potential [28]. In the 2012, a scientist suspected this differential effect of EGCG can be used during treatment of tumors in radiotherapy [6]. Nevertheless, it should be noted that most studies on this topic are preclinical, and that undesirable interactions of EGCG with some anticancer drugs have been described. Therefore, further research, especially at the clinical level, is needed to support the potential role of EGCG as adjuvant in cancer therapy. Thus our research could be useful for developing EGCG as a radioprotector.

There have been no reports of clinical toxicity when green tea is consumed as a beverage throughout the day. Oral pills of green tea polyphenol products are available commercially as dietary supplements. The reported events associated with EGCG consumption include excess gas, upset stomach, nausea, heartburn, stomachache, abdominal pain, dizziness, headache, and muscle pain in the precious studies of health cohort. All of the reported events have been rated as mild events (grade 1). No significant changes were observed in the clinical laboratory measurements. Similar to them, none of the treated patients has experienced a grade III or IV toxicity that was considered related to EGCG. Therefore, an MTD was not defined, and the highest dose tested (based on preclinical data) (440 μmol/L) was defined as the phase II recommended dose. In terms of the effectiveness, an impressive reversal of esophagitis, even during RT continuation and with different concentrations of EGCG, was noted. Although the study was not randomized, its results may allow researchers to conduct preliminary assessments of EGCG efficacy on the ARIE. As described above, we choose mean esophageal dose <34 Gy and the esophageal V50 >30% as an efficient means to screen the patients with Grade II/III esophagitis [29,30]. Statistical analysis showed no significant differences in terms of EGCG concentrations for mean esophagus dose. Grade 2 radiation esophagitis in the selected patients is always expected to progress to grade 3/4 unless RT is interrupted [31]. In the present study, chest RT continued despite the appearance of grade 2 esophagitis. Instead of progression of its severity, a rapid regression of esophagitis was noted in most cases. Recurrent Grade 2 esophagitis occurred in 4 patients in the application of EGCG, and continued treatment was effective in 3 of them at the end of radiotherapy. The reason why Grade 2 radiation esophagitis is sustained in 2 cases during RT may be that different radiosensitivities of endothelial or epithelial cells exist among individuals.

From what has been discussed above, in the absence of adverse effects on normal cells and protective capability in cells exposed to radiation, ECGC can be safely used as a radioprotective agent in radiotherapy and in occupationally exposed individuals. However, some limitations of this study should be underlined. Firstly, no Kuwahata's endoscopic grade of esophagitis was obtained. However, it was not always observed in other studies, and the treatment interruption and QOL decline was mainly due to the clinical symptoms. ARIE progresses to severe (grade III) toxicity, which includes objective interventions such as hospitalization or the need for feeding tube placement. Secondly, we did not take into account the effect on tumor control and chronic esophagitis, which requires further investigation in the recent future. Moreover, the

best way to test the radioprotecting properties of EGCG is by comparing it with placebo. A phase II efficacy study has been initiated at Shandong Cancer Hospital. The eligible criteria are in accordance with the trial. After the occurrence of grade 2 esophagitis, Patients were randomly assigned to one of two treatment arms: EGCG and narcotic agents. The clinical primary endpoint will be resolution of esophagitis and patient-reported pain during the 5-day therapy period. The secondary endpoint was influence of EGCG on the progression free survival (PFS) and objective response rate (ORR). If EGCG could be proven to be a radioprotector without affecting the efficacy of radiation, the ongoing study is testing the use of EGCG with radiotherapy in a variety of cancer including esophageal cancer.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.10.014.

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