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Original article

A prospective phase II trial of EGCG in treatment of acute radiation-induced esophagitis for stage III lung cancer

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ABSTRACT

Background: Acute radiation-induced esophagitis (ARIE) is one of main toxicities complicated by thoracic radiotherapy, influencing patients' quality of life and radiotherapy proceeding seriously. It is difficult to be cured rapidly so far. Our phase I trial preliminarily showed that EGCG may be a promising strategy in the treatment of ARIE.

Materials and methods: We prospectively enrolled patients with stage III lung cancer from the Shandong Tumor Hospital & Institute in China from January 2013 to September 2014. All patients received concurrent or sequential chemo-radiotherapy, or radiotherapy only. EGCG was administrated once ARIE appeared. EGCG was given with the concentration of 440 μmol/L during radiotherapy and additionally two weeks after radiotherapy. RTOG score, dysphagia and pain related to esophagitis were recorded every week.

Results: Thirty-seven patients with stage IIIA and IIIB lung cancer were enrolled in this trial. In comparison to the original, the RTOG score in the 1st, 2nd, 3rd, 4th, 5th week after EGCG prescription and the 1st, 2nd week after radiotherapy decreased significantly ($P = 0.002$, 0.000, 0.000, 0.001, 0.102, 0.000, 0.000, respectively). The pain score of each week was significantly lower than the baseline ($P = 0.000$, 0.000, 0.000, 0.000, 0.006, 0.000, 0.000, respectively).

Conclusion: This trial confirmed that the oral administration of EGCG is an effective and safe method to deal with ARIE. A phase III randomized controlled trial is expected to further corroborate the consequence of EGCG in ARIE treatment.

Lung cancer remains a major public health problem worldwide because of its high incidence, rapid progression, and poor outcome [1]. Patients with stage III non-small cell lung cancer (NSCLC) or limited stage small cell lung cancer (LD-SCLC) are generally treated with sequential chemo-radiotherapy or concurrent chemo-radiotherapy [2,3]. Treatment of lung cancer with radiotherapy, is often accompanied by the development of acute esophagitis. Although advanced delivery techniques, such as 3 dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), have allowed clinicians to reduce the occurrence of acute radiation-induced esophagitis (ARIE) [4–6], ARIE remains the most common dose-limiting acute toxicity, particularly in patients with concurrent chemo-radiotherapy. Options for the prediction [7] and management of clinical ARIE include proton pump inhibitors, antifungal agents, topical anesthetics, antacids [8], amifostine [9], immunomodulatory therapy [10], etc. However, many of these studies came to negative results. Therefore, the treatment strategy of radiation-induced toxicity is attractive both to patients and oncologists.

Green tea extracts can protect normal epithelial cell from carcinogens due to their strong anti-inflammatory and anti-oxidant activities, such as inducing growth arrest, antiangiogenic properties, effects on folate metabolism, effects on DNA damage, inhibition of telomerase, proteasome inhibition or apoptosis and finally cell death [11,12]. Epigallocatechin-3-gallate (EGCG) constitutes about 55–70% of total polyphenols in tea extracts present as the most abundant compound [13–17]. It has been shown that EGCG possesses scavenging activity for the superoxide anion, hydroxyl radical and hydrogen peroxide [18]. Therefore, we conducted a phase I study of EGCG therapy of the esophagus from damage induced by radiation [17]. Twenty-four patients with stage IIIA and IIIB that completed the course of therapy were enrolled in our phase I study. Patients were treated in six cohorts at six dose levels of EGCG.

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Radiotherapy was not interrupted with the median dose of 64 Gy. There were no EGCG-related dose-limiting toxicities reported in all EGCG dosing tiers. Dramatic regression of esophagitis to grade 0/1 was observed in 22 of 24 (91.7%) patients. So we concluded that oral administration of EGCG is feasible, safe and effective.

Based on the results of phase I study, we designed the prospective phase II study to verify the efficacy and safety of EGCG used in the treatment of ARIE.

Materials and methods

This is a phase II study to assess the safety and efficacy of EGCG used in treatment of ARIE in patients receiving sequential or concurrent chemo-radiotherapy. This study was approved by the local ethics board, with registration number of NCT01481818 (www.clinicaltrials.gov). Informed consents were obtained from all patients.

Patients

We prospectively enrolled patients from the Shandong Tumor Hospital & Institute in China from January 2013 to September 2014. All patients were diagnosed of lung cancer pathologically. Patients were required to be staged by the seventh edition of American Joint Committee on Cancer (AJCC), and those with inoperable stage IIIA or stage IIIB were eligible. The inclusion criteria were: age >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. All patients received 3D-CRT or IMRT, 1.8–2.0 Gy per day, 5 days per week, the total dose was planned $\geqslant$60 Gy, the percentages of esophagus volume receiving above 50 Gy (V50) $\geqslant$30%. 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 the esophagus.

Experimental dataset

Therapies received by this cohort included concomitant chemo-radiotherapy, sequential chemo-radiotherapy and radiotherapy only.

All the patients underwent 3D-CRT or IMRT. Vacuum bags were used to improve reproducibility during daily treatments. Three millimeter thick CT scan slices were obtained from Philips Brilliance Big Bore CT and then directly transmitted to the Eclipse treatment planning system (Eclipse 8.6, Varian Medical Systems). The target volume was defined according to International Commission on Radiation Units (ICRU) publications 50 and 62. Gross tumor volume (GTV) included primary tumor and metastatic regional lymph nodes observed on CT scans. Clinical target volume (CTV) included GTV and 0.3–0.5 cm margin, but stopped when encountered an anatomy barrier. Planning target volume (PTV) included CTV and 0.5–1.0 cm margin for lymph nodes, 0.8–1.5 cm for the primary tumor. For the purpose of consistency the organs at risk (OARs) were contoured in all patients by the same radiation oncologists. Dose distribution was calculated with tissue heterogeneity correction in the treatment planning system. The total dose was planned at 60–66 Gy in 30–33 fractions over 6–7 weeks based on the condition of lung, cardiac, etc. The radiation dose was prescribed to the edge of PTV with a minimum target dose of 95% and a maximum dose of 105%. The entire esophagus was contoured from the border of the cricoid cartilage to the gastro-esophageal junction in each patient. The dose constraints were: mean lung dose (containing the primary tumor) $\leqslant$18 Gy, V20 of lung $\leqslant$30%, the maximum spinal cord $\leqslant$50 Gy, total heart $\leqslant$35 Gy.

EGCG preparation and prescription

On the basis of our previous research results, the 440 μmol/L concentration was defined as the dose for this phase II trial. EGCG (NINGBO HEP Biotech Co., Ltd) was dissolved in 0.9% saline solution and stored at 4 °C. The purity of EGCG was required to be above 95% as analyzed by RP-HPLC. For esophageal application, slow swallowing of 15 ml EGCG solution was required to assure the prolonged presence of the drug on the esophageal walls. EGCG was given with the concentration of 440 μmol/L three times a day during the radiation.

Study design and treatment

The treatment with the EGCG solution was given to patients on the same day when ARIE appeared (this time was also considered as the original time point). From then on, every week we recorded RTOG score, patient-reported pain and dysphagia related to esophagitis (all were the highest scores of the very week), which were measured using Toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC), numerical rating scale (NRS) and Common Terminology Criteria for Adverse Events (CTCAE), respectively. And we also recorded the time point and the dose of RT when grade 1 ARIE occurred. EGCG was given with the concentration of 440 μmol/L three times a day. And it was given during radiotherapy and additionally two weeks after radiotherapy.

Steroids, non-steroidal anti-inflammatory drugs, narcotics, local anesthetics, or other antibiotic/antifungal therapy were not given until esophagitis progressed to grade 3. RT was not interrupted unless persistent or deteriorating symptoms were present after therapy. In cases that RT was suspended, patients were supported with methylprednisolone, analgesics, antifungal therapy, or intravenous fluid administration as appropriate therapy until recovery. Nasogastric tubes were to be used only in unresponsive patients whose grade 4 toxicity persisted above 3 days after toxicity documentation.

Toxicity assessment

During the course of radiotherapy, patients were inquired and examined weekly. Acute toxicities related to EGCG were scored prospectively using RTOG/EORTC and were evaluated from the start of treatment to 1 month after radiotherapy. Toxicities were scored at the baseline and weekly during radiotherapy until 4 weeks after treatment. The items scored included: nausea & vomiting; dysphagia; anorexia; weight loss; constipation; dyspnea, cough and pain. Thereafter, patients were followed up at one month intervals or more frequently if indicated.

Statistical analysis

The primary endpoint of the study was the clinical response rate. The response rate was defined as the number of grade 0 patients in every week expressed as a percentage of the sample in that week. We used SPSS statistical software, version 13.0, for statistical analysis. The differences of RTOG score and dysphagia score among different weeks were tested using Wilcoxon matched-pairs signed-ranks test. The differences of pain score among different weeks were tested using paired-samples t test. All statistical tests were conducted at a two-sided level of significance of 0.05.

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