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Editorial

EGCG, a green tea polyphenol, as one more weapon in the arsenal to fight radiation esophagitis?

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Radiotherapy (RT) is a mainstay in the treatment of locally advanced non-small cell lung cancer (NSCLC). The addition of chemotherapy (CHT) to RT improves the survival of patients with NSCLC [1]. A concurrent approach is superior to a sequential CHT-RT approach in patients with PS 0–1 and stage III NSCLC [2]. If, for any reason, CHT cannot be given to such patients, the hyperfractionated acceleration of RT improves the treatment outcome compared with conventional fractionation [3]. However, these more efficacious treatment modalities are also more aggressive, i.e., more toxic. Grade 3 or 4 radiation esophagitis is more frequent in concurrent RT-CHT than in sequential CHT-RT or RT alone. A meta-analysis of six randomized trials that compared concurrent RT-CHT with sequential RT-CHT showed that severe (grade 3–4) radiation esophagitis occurred in 18% of concurrent approaches compared with 4% in sequential approaches, respectively, with a relative risk of 4.9 ($p < .001$) [2]. In addition, accelerated RT increases the risk of severe acute esophagitis by 2.4 ($p < .001$) compared with conventional fractionation [3]. Clinically significant radiation esophagitis is a common event during concurrent RT-CHT for lung cancer. An individual-patient-data meta-analysis that included 1082 patients who received concurrent radical RT-CHT for NSCLC demonstrated that grades 2, 3, and 4 esophagitis occur in 32.2%, 17.1%, and 0.9% of patients, respectively, with no radiation esophagitis-related deaths [4]. Despite the fact that radiation esophagitis is very rarely life-threatening, its bothersome symptoms may cause treatment interruptions and even earlier treatment terminations without the delivery of the prescribed total radiation dose, which could compromise the outcome of potentially curative treatments.

Therefore, the search for radioprotectors (compounds administered before or at the time of irradiation to minimize radiation damage to normal tissues) or radiation mitigators (compounds that decrease radiation toxicity when administered before the onset of toxic effects) is worthwhile. So far, the only radioprotector approved by the U.S. Food and Drug Administration (FDA) is amifostine, a drug that exhibits radioprotection by scavenging the free radicals generated by ionizing radiation and prevents their interaction with DNA in healthy tissues. However, due to its narrow therapeutic window and limitations of clinical trials, the panel of ASCO experts does not recommend its use in RT-CHT in NSCLC for the prevention of esophagitis [5]. The failure of synthetic compounds to prevent radiation toxicity efficiently led to growing interest in the study of natural radioprotectors derived from nontoxic plants that are recognized as remedies for various medical problems in traditional medicine [6]. Traditional Ayurvedic medicine indicates sweet and bitter herbs as well as nutrition to diminish inflammation for the prevention of early radiation-induced esophagitis [7]. Derivatives of natural products include polyphenols such as catechins, which are thought to contribute to the health benefits of green tea. Epigallocatechin-3-gallate (EGCG) is a green tea catechin that has the ability to scavenge free radicals and may protect healthy tissues from radiation effects. Additionally, its ability to intercalate with DNA protects it from free radical damage by stabilization of double-stranded DNA; thus, it may have preventive effects also by this mechanism. EGCG may also be active as a radiation mitigator and may delay the onset of radiation adverse effects or decrease their intensity [8,9]. Therefore, a double benefit—the prevention of and treatment for toxicity—may be expected from the use of EGCG during radiotherapy.

In this issue of *Radiotherapy & Oncology*, Zhao et al. [10] report the results of a phase III trial that evaluated the efficacy of EGCG in the prevention of and treatment for radiation-induced esophagitis in patients receiving RT-CHT for lung cancer. This team has a long-standing interest in introducing EGCG as a radioprotector in clinical practice. First, in a phase I trial in 24 patients receiving concurrent RT-CHT for locally advanced NSCLC, they confirmed the safety of oral administration of this agent during radiotherapy. In addition, regression of grade 2 radiation esophagitis to grade 0–1 was observed in 22 of the 24 patients [11]. They then prospectively conducted a single-arm phase II trial using EGCG in 37 patients with lung cancer undergoing radiotherapy. EGCG started during radiotherapy at a concentration of 440 μmol/L when the symptoms of acute esophagitis occurred and continued to two weeks after completion of radiotherapy. All measures of acute esophagitis decreased significantly within two weeks following the prescription of EGCG [12].

Encouraged by these results, Zhao et al. [10] evaluated now the efficacy of EGCG in the prevention of and treatment for acute radiation esophagitis in lung cancer patients receiving combination

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(concurrent or sequential) RT-CHT in locally advanced NSCLC or limited stage SCLC in a three-arm prospective randomized study. Patients in the prophylactic experimental arm A ($N = 28$) received EGCG orally from the start of radiotherapy. Patients in therapeutic experimental arm B ($N = 27$) received EGCG at the onset of mild signs of radiation esophagitis. Patients in the control arm C ($N = 28$) received conventional (standard) medication from the appearance of mild signs of radiation esophagitis. Conventional medication consisted of a mixture of lidocaine, dexamethasone, and gentamycin (mLDG). No significant differences in esophageal dose metrics were found among the three groups, but a significant difference in the maximum intensity of acute esophagitis was observed among the three arms ($p = .004$). The difference in esophagitis did not reach statistical significance between the prophylactic (A) and therapeutic (B) application groups ($p = .054$); however, the maximum intensity of esophagitis was lower for patients in arms A and B than for those in the control arm ($p = .036$). The mean acute esophagitis index (AEI) was significantly lower in the prophylactic EGCG arm than in the therapeutic EGCG arm, and the mean AEI was lower in the group receiving therapeutic EGCG than in the group receiving conventional medication (control group). Based on these findings, the authors concluded that EGCG could safely and effectively prevent and alleviate acute radiation esophagitis in RT-CHT for lung cancer. Prophylactic application of EGCG appeared to have a slight advantage over its therapeutic use. The authors nicely enumerated the limitations of their findings, which included a relatively small sample size, the heterogeneity of the radiation total dose and RT-CHT schedule among the arms (even though these were not significantly different when pretreatment characteristics were evaluated), no consideration of tumor volume, and an unconscious bias toward experimental agents that could not be completely ruled out. Similar to other studies on radioprotectors, the question about the potential negative impact of EGCG on local control arises, since radioprotection may, to some extent, also concern cancer cells. A recently published study by Jung et al. [13] for example suggests that antioxidant use during chemotherapy or radiation therapy was associated with worsened breast cancer prognosis in postmenopausal women. In the presented study, no significant difference in the response rate was found among the three groups; however, it needs to be clearly stated that the study is statistically not powered and follow up was not sufficiently long to detect even clinically highly important differences. Further studies are therefore warranted to affirm the benefits of EGCG and to exclude harm to patients in terms of decreased chances for local tumor control. Nevertheless, the good compliance and no obvious side effects make EGCG a very attractive agent for future clinical investigations.

Obviously, radiation oncologists have also other means to limit radiation esophagitis, including the use of novel technologies, accurate imaging, and careful planning to reduce the radiation dose delivered to the esophagus. Efforts to deliver high doses to the esophagus should be prioritized. However, we still have no robust model for the prediction of esophageal toxicity after RT-CHT. Further studies are needed to validate normal tissue complications probability models for the prediction of acute radiation esophagitis [14]. Generally, grade 3 acute radiation esophagitis is associated with the mean esophageal dose, V60, and neutropenia. However, due to the potential benefits of concurrent RT-CHT in NSCLC, total dose reductions are not recommended because esophagitis usually heals within 3–5 weeks, and the survival benefit of the combined approach outweighs any temporary patient suffering [15]. On the other hand, for patients treated with palliative intent for NSCLC, the issue of esophageal side effects should not be neglected. Their symptom burden should not be increased by radiation side effects. Recently, it was demonstrated in a multicenter prospective trial that esophageal toxicity was decreased by using careful 3-D planning in order to reduce doses to the esophagus for patients treated with palliative radiotherapy (39 Gy in 13 fractions, 20 Gy in 5 fractions, and 17 Gy in 2 fractions) [16].

The findings of Zhao et al. [10] are quite unique because they suggest a potential value of a derivative of a substance recognized by traditional medicine in alleviating radiation-induced side effects. Before recommendations can be made for clinical practice, future studies which are sufficiently powered to also assess potential negative effects on the tumor, need to establish whether EGCG is widening the therapeutic index.

Declaration of Competing Interest

None.

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