

RESEARCH ARTICLE

Clinical Investigation in Effect of Riboflavin Sodium Phosphate on Prevention and Treatment for Patients with Radiotherapy Related Esophagitis

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Abstract

Objective: To investigate the clinical effect of riboflavin sodium phosphate on prevention of radiotherapy related esophagitis (RRE). **Methods:** This retrospective study involved 55 patients with middle and advanced esophageal cancer who were divided into an experimental group of 28 and a control group of 27 patients. Those in the experimental group were treated with riboflavin sodium phosphate combined with conventional symptomatic treatment during radiotherapy; while patients in control group received the latter alone. The incidence and degree of RRE were compared after radiotherapy. **Results:** The incidences of RRE in experimental and control group were 53.5% and 81.4%, respectively ($p < 0.05$); the incidence of stages III and IV RRE in the experimental group was 17.8%, while in the control group it was 44.4% ($p < 0.05$). **Conclusion:** Riboflavin sodium phosphate could significantly prevent RRE and reduce the incidence of stage III and IV disease. These results were worthy of further confirmation by randomized controlled trials.

Keywords: Riboflavin - esophageal cancer - radiotherapy - esophagitis - prevention

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Introduction

Esophageal cancer is a common malignant tumor in China, according to a report from World Health Organization, about 50% of esophageal cancer occurred in China. Radiotherapy is a standard treatment for middle and advanced radioactive esophageal cancer that can not be cured with surgery. Radiotherapy related esophagitis (RRE), one of the most common complications in the process of esophageal cancer treatment with an incidence of about 85%, is a main symptom for patients in this cohort. RRE even affects the treatment for patients due to interruption of treatment and negatively influences the treatment effect of radiotherapy. Choy reported that compared with radiotherapy alone, concurrent chemo- (chemotherapy consisted with carboplatin and paclitaxel) and radiotherapy (total dose 66 Gy, 2 Gy /day) could significantly reduce the tolerance of esophagus, and is associated with an occurrence of acute esophagitis at an incidence as high as 46% (Choy et al., 2005). Hence, prevention and treatment of RRE should be carefully considered in the process of radiotherapy for patients with esophageal cancer. This retrospective study enrolled patients with middle and advanced esophageal cancer in 2013. In the study, we hypothesized that riboflavin sodium phosphate by intravenous infusion could prevent and treat patients with RRE.

Materials and Methods

Inclusion criteria

Patients recruited in this study were required to be pathologically/cytologically diagnosed with esophageal cancer; to sign an informed consent before treatment; to expose to chemo- or radiotherapy; to have staged III or IV ESCC and not indicated for surgery, and a score of karnofsky performance status (KPS) ≥ 50 with expectancy life span more than 3 months; with no contraindications for chemo-, radiotherapy. The exclusion criteria included the following: pregnant or nursing women; hemoglobin ≤ 100 g/L, leucocyte $\leq 3.6 \times 10^9$ /L, platelets count $\leq 10 \times 10^{11}$ /L, and hepatic or renal function abnormal.

Methods

Before treatment, all measurable lesions were documented by chest, upper abdominal computed tomography (CT) scan, bone scanning or other necessary examination. Three-dimensional conformal treatment was recommended when radiotherapy was conducted as the following: (1) We take gross tumor volume (GTV) as the primary lesions which referenced the length from esophagography, esophagoscopy and/or intracavity ultrasound. While CTV included GTV and lymphatic drainage area, which extended 0.8 cm on the left and right

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based on GTV and extroverted 3 to 5 cm on upper and lower. planning target volume (PTV): 0.5cm extroverted on the basis of the GTV. (2) Radiation dosage of 95% PTV were 2 Gy per dose and 5 doses per week and a total of 60 Gy. Riboflavin sodium phosphate 10mg was administrated by intravenous infusion for patients in experimental group. Patients without the administration of riboflavin sodium phosphate entered control group. During the treatment, patients were monitored for signs or symptoms of hematologic, pulmonary, or gastrointestinal toxicity every week. When Grade ≥ 3 toxicities were observed, supportive therapy was provided and appropriate adjustments to the radiotherapy were made, including withholding the treatment.

Observation evaluation criteria

Treatment assessment

All patients should be followed up till disease progression, which was confirmed by imaging technology, and record of time to progression. Evaluation of response was carried out according to RECIST criteria, including complete response (CR), partial response (PR), stable (SD) and progress (PD), overall response rate (RR)= CR + PR. Adverse reaction was evaluated according to National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTC).

According to staging criteria of RTOG acute radiation esophagitis, stage 0: no change; stage I: mild dysphagia or swallowing pain, requiring surface anesthetic or non anaesthetic for analgesia or half liquid diet; stage II: moderate dysphagia or swallowing pain, requiring anesthetic for analgesia or liquid diet; stage III: severe dysphagia or swallowing pain, with dehydration or weight loss greater than 15%, requiring nasal feeding or intravenously nutrimental supplement; stage IV: complete obstruction, ulcer, perforation or sinus formation.

Data statistics

Using SPSS10.0 for data analysis, count data were compared with X² test. P< 0.05 was defined as statistical significance.

Results

Fifty five patients (aged 42-73, average age of 54.3 years; PS core ranging from 0 to 1) with middle and advanced esophageal cancer treated in our department from June 2013 to December 2013 were enrolled and divided into experimental group with 28 and control group with 27 patients.

The incidence of RRE in experimental control group was 53.5%, and 81.4% in control group (X²=4.86), respectively. The incidence of stage III and IV RRE was 17.8% in experimental, while 44.4% in control group respectively (X²=4.55, p< 0.05) (Table 1).

Discussion

In China, about 95% of patients with esophageal cancer were pathologically diagnosed with squamous cell carcinomas who could achieve treatment response

by radiotherapy. With the development of technology, three-dimensional conformal radiotherapy has become a mainstay for treating patients with esophageal cancer. Although three-dimensional plan system allows clinician to reduce the volume and dosage of radiation on esophagus, normal esophageal tissue could not be completely ruled out of radiation field. The quality of life for these patients could be destroyed by clinical symptoms accompanied with radioactive esophagitis, eg., dysphagia or swallowing pain. However, conservative treatment is very difficult to achieve rapid recovery of RRE so that patients could not tolerate further treatment (Huang et al., 2014; Qian et al., 2014). As a consequence, an effective clinical method is urgently needed to prevent and treat RRE. RRE is closely associated with the total dose of radiation. When accumulated dose of radiation reaches 10-29GY, patient will have swallowing pain and a burning sensation in esophagus during eating. Gastroscope usually suggests mucosal hyperemia, edema, exudation and erosion on the examination.

It was revealed from this study that the typical clinical symptoms of RRE included aggravating dysphagia, local pain and retrosternal burning sensation, especially serious when eating. Reported medications that could be considered for treating acute toxicities of concurrent radiotherapy or chemoradiotherapy, as well as RRE including supportive care, eg., antibiotics, and vitamins (Bostrm et al, 2001; Liu et al., 2014; Tian et al., 2014; Wang et al., 2014; Xiao et al., 2014). Riboflavin, commonly known as vitamin B2, with a biological activity mainly involving two flavin coenzymes, namely flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), combining these two flavin coenzymes forming flavor protein with other proteins. Biologically oxidative reactions were involved in vivo and energy metabolism (Wojcieszynska D et al, 2012; Vasilaki A T et al, 2010). This is a major enzyme system for activation or detoxifying of chemical carcinogens. As a result, antioxidant function could be directly weakened because of lack of riboflavin, while antioxidant function would be strengthened when riboflavin is supplemented. Digestive ulcer usually occurs in cancer patients during the period of radiotherapy or chemotherapy, and frequently causes systemic infection when ulcer is serious. Previous research suggested that riboflavin could prevent and treat radiotherapy or chemotherapy related gastrointestinal mucositis (Serrano A et al, 2012; Makdoui K et al, 2013; Gatzioufas Z et al, 2010; Xuan Z et al, 2013). But no report on prevention and control of RRE was found. The results of our current study demonstrate that the incidence and degree of RRE could be decreased and symptoms of patients could be alleviated significantly by supplementing exogenous

Table 1. Incidence of Adverse Reaction of Radioactive Esophagitis

	Stage						Incidence (%)	
	Number of patients	0	I	II	III	IV	Incidence (%)	Stage III and IV
Experimental group	28	13	7	3	5	0	53.5	17.8
Control group	27	5	4	6	9	3	81.4	44.4

riboflavin at the beginning of radiation. And provides good support to complete radiotherapy and improves tumor local control. In conclusion, riboflavin sodium phosphate could significantly prevent and control RRE and reduce the incidence of radioactive esophagitis III and IV, worthy of being confirmed by further randomized controlled trials.

fluvoxamine combined with oxycodone prolonged-release tablets in treating patients with moderate to severe cancer pain. *Asian Pac J Cancer Prev*, **15**, 10445-9.

Xuan Z, An Y, Yang D, et al (2013). Exploration of the protection of riboflavin laurate on oral mucositis induced by chemotherapy or radiotherapy at the cellular level: what is the leading contributor. *Int J Mol Sci*, **14**, 4722.

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References

- Bostrm A, Lindman H, Swartling C, et al (2001). potent corticosteroid (mometasone furoate cream) significantly reduces acute radiation dermatitis: results from a double-blind randomized study. *Radiother Oncol*, **59**, 257-65.
- Choy H, Vokes E (2005). Improving outcomes in the treatment of locally advanced NSCLC with gemcitabine. *Lung Cancer*, **50**, S10-2
- Gatzioufas Z, Seitz B (2010). Riboflavin-UVA treatment for nonhealing ulcers of the cornea. *J Refract Surg*, **26**, 312.
- Huang XE, Cao J, Qian ZY, et al (2014). Leucogen tablets at 60 mg three times per day are safe and effective to control febrile neutropenia. *Asian Pac J Cancer Prev*, **15**, 8495-7.
- Liu J, Huang XE (2014). Efficacy of bifidobacterium tetragenous viable bacteria tablets for cancer patients with functional constipation. *Asian Pac J Cancer Prev*, **15**, 10241-4.
- Makdoui K, Mortensen J, Crafoord S (2013). Response to: Evaluation of combined riboflavin and ultraviolet A as an alternative treatment for keratitis. *Graefes Arch Clin Exp Ophthalmol*, **251**, 997.
- Qian YD, Xu X, Wang L, et al (2014). Clinical safety of chemotherapy for elderly cancer patients complicated with hypertension. *Asian Pac J Cancer Prev*, **15**, 9875-7.
- Russo G, Haddad R, Posner M, et al (2008). Radiation treatment Breaks and ulcerative mucositis in head and neck cancer. *The Oncologist*, **13**, 886-98.
- Serrano A, Frago S, Velázquez-Campoy A, et al (2012). Role of key residues at the flavin mononucleotide (FMN):adenylyltransferase catalytic site of the bifunctional riboflavin kinase/flavin adenine dinucleotide (FAD) Synthetase from *Corynebacterium ammoniagenes*. *Int J Mol Sci*, **13**, 14492.
- Tian GY, Miu M, Huang XE et al (2014). Systematic analysis of pemetrexed-based chemoradiotherapy for patients with locally advanced or metastatic esophageal cancer. *Asian Pac J Cancer Prev*, **15**, 8475-8.
- Vasilaki A T, McMillan D C, Kinsella J, et al (2010). Relation between riboflavin flavin mononucleotide and flavin adenine dinucleotide concentrations in plasma and red cells in patients with critical illness. *Clin Chim Acta*, **411**, 1750.
- Wang L, Huang XE (2014). Clinical study on safety and efficacy of jisaixin (recombinant human granulocyte colony stimulating factor injection manufactured in China) for chinese undergoing chemotherapy. *Asian Pac J Cancer Prev*, **16**, 299-301.
- Wojcieszynska D, Hupert-Kocurek K, Guzik U (2012). Flavin-dependent enzymes in cancer prevention. *Int J Mol Sci*, **13**, 16751
- Xiao Y, Liu J, Huang XE, et al (2014). Clinical study on