The Predictive Role of Serum Gastrin-17 for Oral Mucositis in Head and Neck Carcinoma Patients Receiving Radiotherapy

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Abstract

Objective

The aim of this study was to analyze the predictive role of serum gastrin-17 (G-17) for oral mucositis in head and neck carcinoma (HNC) patients receiving radiotherapy.

Methods

Serum G-17 were detected in patients before and after radiotherapy. Patients were divided into high G-17 group (baseline serum G-17 ≥ 5pmol/L) and low G-17 group (baseline serum G-17 < 5pmol/L). The severity of oral mucositis was analyzed between the two group. Other complications such as dysphagia, salivary gland, mandible, thyroid function, larynx, pain, and weight loss were also investigated.

Results

Forty-two patients were analyzed in this study. The median level of serum G-17 had a significant decrease after radiotherapy (7.29 ± 5.70 pmol/L versus 4.93 ± 4.46 pmol/L, P = 0.038). In low serum G-17 group, the incidences of grade 0, 1–2 and 3–4 of oral mucositis were 0%, 30.4%, and 69.6%, respectively. In high serum G-17 group, the incidences of grade 0, 1–2 and 3–4 of oral mucositis were 0%, 63.2%, and 36.8%, respectively. Pearson correlation analysis showed that serum G-17 was negatively correlated with oral mucositis (r=-0.595, P < 0.01). Weight loss of low G-17 group was more serious than that of high G-17 group.

Conclusions

Baseline serum G-17 is a potential predictor for the severity of oral mucositis in HNC patients receiving radiotherapy.

Introduction

Annually, nearly 900,000 patients are diagnosed with head and neck carcinoma (HNC)[1]. Although combined methods in modern oncology have made rapid progress, radiotherapy remains a primary treatment for patients with HNC[2]. About 80% of patients need radiotherapy at different stages of treatment. Precise radiotherapy can effectively improve the local control rate and cure rate of the tumor, but the normal tissues such as parotid gland, cerebrospinal cord and cranial nerve around the tumor will receive a certain dose of radiation. Acute complications such as oral mucositis, swallowing disorders, xerostomia and skin pain emerge in varying degrees, leading to impaired quality of life and malnutrition[3].

Oral mucositis is a common side effect of chemotherapy and radiotherapy. The incidence is about 85–100% in HNC patients receiving radiotherapy[4]. Previous studies have shown that the severity of oral mucositis is affected by radiotherapy mode, low body mass, prolonged neutrophil recovery, and young age[5, 6]. As oral mucositis can cause reduced food intake, which may affect gastric acid secretory capacity, we initially intended to retrospectively analyze the relationship of gastric functions with food intake. The gastric functions including serum gastrin-17 (G-17), pepsinogen I (PG-1), pepsinogen II (PG-II) and the ration of PG I/PG II have been widely used in clinic. The baseline serum G-17 seemed relatively lower in patients with severe oral mucositis. This study aimed to investigated the relationship of serum G-17 and oral mucositis in HNC patients underwent radiotherapy.

Methods

Patients

Between January 2018 to December 2020, 76 HNC patients received radiotherapy at the Departments of oncology, Nanjing First hospital. This retrospective study included patients who detected gastric function before and after radiotherapy. Exclusion criteria included chronic and acute gastric diseases, ECOG score 1, receiving enteral nutrition and/or PPI, and insufficiency of the data. Forty-two patients were left for analysis. For each patient in this study, data were recorded on standard admission proformas and supplemented by retrospective chart review from the hospital laboratory database. Details of age, sex, history of smoking, performance status, tumor characteristics including site and stage distribution, and treatment modalities were noted.

Treatment modalities

Primary radiotherapy was generally delivered in 5 fractions of 2Gy each, for a total dosage of 70Gy. Chemoradiation was consisted of cisplatin 100 mg/m^2 on days 1, 22 and 43 concomitantly with conventionally fractionated radiotherapy as primary radiotherapy alone. Postoperative radiotherapy was given at a total dose of 56 to 66Gy depending on the presence of high-risk factors.

Complications

Acute toxicities were categorized according to the Common Terminology Criteria (CTC) for AEs, version 3.0 (< 90 d posttreatment). Toxicities were coded for mucosa, skin, dysphagia, pain, weight loss, xerostomia, and larynx.

Test of gastric function

The tests of serum G-17, PG-I, and PG-II were determined by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Fasting blood samples were taken before and after radiotherapy within 1 week. Fresh samples were sent on schedule to the Department of Clinical Laboratory, and serum was examined the same day. The cutoffs of normal references were, G-17 1–

15pmol/L, PG-I 70–165 ug/L, PG-II 3–15 ug/L, and PG-I/II ratio 7–20, respectively. Patients were divided into two groups based on their baseline serum G-17 levels: low group (G-17<5pmol /L) and high group (G-17≥5pmol /L).

Statistics

Statistical analysis was performed using SPSS version 18 statistical software. Continuous variables were expressed as mean ± SEM or as medians with interquartile rang, and are analyzed with two tailed *t* test for normal distributions and the Mann-Whitney U test for non-normal distributions. Categorical data were analyzed by using $\chi 2$ test or Fisher's exact test as appropriate. Pearson correlation analysis was performed to identify the relationship of serum G-17 and oral mucositis. A *P* value < 0.05 was considered to be of statistical significance.

Results

Patients' characteristics

Among the 42 patients, 33 patients were male. The mean age of the study population was 62.2 ± 13.2 years. The median follow-up for all patients was 15 months. Table 1 listed patient demographics, including sex, age, smoking history, performance status, tumor characteristics including site and stage distribution, and treatment modalities. The median cumulative radiation dose was 64.8 ± 4.5Gy, and the median treatment duration was 45.3 ± 3.8 days.

Table 1
The Baseline characteristics of patients before radiotherapy

Characteristics	Number(%)
Age	
18–60 years	14(33.3)
>60 years	28(66.7)
Sex	
Male	32(76.2)
Female	10(23.8)
Smoking	
Smoker	29(69.0)
Nonsmoker	13(31.0)
ECOG performance status	
0	33(78.6)
1	9(21.4)
Tumor site	
Nasopharynx	17(40.5)
Oral cavity	6(12.3)
Oropharynx	5(11.9)
Hypopharynx	2(4.8)
Larynx	12(28.6)
T stage of primary tumor	
T1	13(31.0)
T2	15(35.7)
T3	9(21.4)
T4	5(11.9)
Nodal stage	
N0	18(42.9)
N1	14(33.3)

Characteristics	Number(%)
N2	6(14.3)
N3	4(9.5)
treatment modality	
Radiotherapy conventional fractionation	9(21.4)
Postoperative radiotherapy	12(28.6)
Chemoradiation	21(50.0)

The Change Of Serum G-17

The levels of serum G-17, pepsinogen I, pepsinogen II and the ration of PG I/PG II before and after radiotherapy were shown in Table 2. The median level of serum G-17 had a significant decrease after radiotherapy (7.29 ± 5.70pmol/L vs. 4.93 ± 4.46pmol/L, $P = 0.038$). No significant changes in PG I, PG II and the ration of PG I/PG II were observed.

Table 2
The serum values of gastric function before and after radiotherapy

	Before radiotherapy	After radiotherapy	*P*
gastrin-17, pmol/l	7.29 ± 5.70	4.93 ± 4.46	0.038
pepsinogen I, ug/L	141.44 ± 91.58	123.61 ± 78.82	0.342
pepsinogen II, ug/L	19.80 ± 13.84	15.14 ± 14.7	0.138
pepsinogen I/II	10.11 ± 11.83	11.43 ± 11.04	0.533

The Relationship Of Oral Mucositis And Serum G-17

The results of oral mucositis and serum G-17 were shown in Table 3. For patients with baseline serum G-17 < 5pmol/L, the incidences of grade 0, 1–2 and 3–4 of oral mucositis were 0%, 30.4%, and 69.6%, respectively. For patients with baseline serum G-17 ≥ 5pmol/L, the incidences of grade 0, 1–2, and 3–4 of oral mucositis were 0%, 63.2%, and 36.8%, respectively. Low serum G-17 group had a significantly higher incidence of severe oral mucositis than that of high serum G-17 group ($P = 0.034$). For the whole group, the baseline level of G-17 in patients with grade 3–4 oral mucositis was 4.74 ± 3.33pmol/L, which was significantly lower than the result of 9.84 ± 6.47pmol/L in patients with grade 1–2 oral mucositis. Pearson correlation analysis showed that serum G-17 was negatively correlated with oral mucositis (r=-0.595, $P < 0.01$).

Table 3
The incidences of oral mucositis between low and high G-17 groups

	Low G-17 group, n = 23	High G-17 group, n = 19	*P*
RF dose, Gy	65.5 ± 8.6	63.5 ± 7.3	> 0.05
Primary radiotherapy	5(21.7)	4(21.1)	> 0.05
Postoperative radiotherapy	6(26.1)	6(31.6)	> 0.05
Chemoradiation	12(51.2)	9(47.4)	> 0.05
Oral mucositis Grade			
1–2	7(30.4%)	12(63.2%)	0.034
3–4	16(69.6%)	7(36.8%)	

Other Complications

The other short complications after radiotherapy between high serum G-17 group and low serum G-17 group were listed in Table 4. There were no significant differences in skin, dysphagia, pain, xerostomia and larynx. The grade 0,1–2 and 3–4 of weight loss in low serum G-17 group were 3 (13.0%), 12 (52.1%) and 8 (34.8%), respectively. The results in high serum G-17 group were 5 (26.3%), 11 (57.9%) and 3 (15.8%), respectively. Correspondingly, the magnitude of decrease in body weight loss was higher in Low-G-17 group than that in high-G-17 group (17.9 ± 7.3% vs. 14.7 ± 5.9%, *P* = 0.13).

Table 4
The incidences of other complications of radiotherapy between low and high G-17 groups

	Low G-17 group, n = 23			High G-17 group, n = 19		
	Grade			Grade		
	0	1–2	3–4	0	1–2	3–4
Skin	2(8.7)	13(56.5)	9(39.1)	3(15.8)	11(57.9)	5(26.3)
Dysphagia	5(21.7)	10(43.5)	8(34.8)	4(21.1)	9(47.4)	6(31.6)
Pain	11(47.8)	12(52.2)	0(0)	11(57.9)	8(42.1)	0(0)
Weight loss	3(13.0)	12(52.1)	8(34.8)	5(26.3)	11(57.9)	3(15.8)
Xerostomia	6(26.1)	14(60.9)	3(13)	3(15.8)	13(68.4)	3(15.8)
Larynx	18(78.3)	5(21.7)	0(0)	15(78.9)	4(21.1)	0(0)

Discussion

Oral mucositis is a common complication in almost all HNC patients underwent radiotherapy[2]. It reduces the quality of life and requires more care. How to identify patients who are prone to oral mucositis is crucial in the therapy process. The results of this study show that serum G-17 has close relationship with oral mucositis in HNC patients. Baseline serum G-17 before radiotherapy may be a potential predictor for the severity of oral mucositis.

Serum G-17 is a noninvasive biomarker reflecting the structure and functional status of gastric mucosa[7, 8]. It is only secreted by G cells in the gastric antrum. The secretion is mainly affected by the pH value in the stomach, the number of G cells and food intake. It is a sensitive indicator reflecting the secretion function of gastric antrum and is used for screening and diagnosing atrophic gastritis and gastric cancer[9]. In this study, we observed that the level of serum G-17 decreased after radiotherapy. This may be caused by decreased food intake and atrophy of gastric antrum.

Oral mucositis is an inflammatory reaction characterized by cytokines with a pro-inflammatory profile. Gastrin can promote the growth of normal gastrointestinal mucosa and maintain gastrointestinal mucosal integrity[10]. Barrett's esophagus is an acquired condition resulting from severe esophageal mucosal injury. Previous study shown that the serum levels of G-17 are lower in patients with Barrett’s esophagus (BE) than in non-BE controls[11]. G-17 significantly promote cell growth and DNA synthesis via CCK-2 receptor-mediated cyclooxygenase-2 induction and prostaglandin E2 production[12]. As we know, cyclooxygenases and prostaglandins play key role in mucosal protection in the gastrointestinal tract[13]. Suppressing cyclooxygenase-2 expression can reduce the severity of radiation-induced oral mucositis[14]. This may explain why low serum G-17 group has more serious oral mucositis after radiotherapy.

Weight loss and malnutrition are secondary disorders in patients diagnosed with HNC[15]. In gastric bypass models, gastrin infusion can prevent mucosal atrophy and attenuate the body weight reduction[16]. In a systematic review, the authors found there were limited data about nutritional impact symptoms outcomes available for HNC patients[17]. However, severe oral mucositis induced by radiotherapy can directly lead to reduced food intake, malnutrition and weight loss. Many studies have investigated interventions to mitigate oral mucositis and body loss[18, 19]. Catrina et al[18] identified twenty-four studies, the role of benzydamine hydrochloride mouth rinse and honey were not recommended due to the overall low quality of the studies and weak evidence supporting the intervention. Although the authors recommended glutamine to mitigate oral mucositis, there is also a need for high-quality studies with a consensus of the methodology to reduce heterogeneity. According to Amanda et al[20], photobiomodulation for oral mucositis also shown positive impact to reduce weight loss and prevented a reduction in BMI in HNC patients who underwent chemoradiotherapy. Relieving oral mucositis can improve weight loss and nutritional status.

This study has some limitation that should be noted. The limited sample size needs more work to be done to verify and confirm the results. however, this small sample size is also meaningful because it harkens back to a more inspiring trend. The result can inspire further researches on how to alleviate oral

mucositis in HNC patients receiving radiotherapy. Gastroscope combined with serum G-17 before radiotherapy may be used to assess patients' stomach function and risk of oral mucositis.

In conclusion, serum G-17 has a close relationship with the severity of oral mucositis. Identifying patients who are prone to oral mucositis before radiotherapy is helpful to devote more attention to care and make nutrition plan for NHC patients.

Declarations

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Code availability: N/A

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