The effects of recombinant human granulocyte colony-stimulating factor mouthwash on radiotherapy-induced oral mucositis in locally advanced nasopharyngeal carcinoma patients

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Abstract

Background. Acute oral mucositis is a common complication of radiotherapy for nasopharyngeal carcinoma (NPC) patients.

Objectives. The aim of the study was to observe the effects of recombinant human granulocyte colony-stimulating factor (rhG-CSF) on radiotherapy-induced oral mucositis in locally advanced NPC patients.

Material and methods. The study involved 64 locally advanced NPC patients that were randomly allocated to receive either rhG-CSF mouthwash (2 µg/mL rhG-CSF; group A, n = 34) or a compounded mouth rinse (10 µg/mL vitamin B12, 0.48 mg/mL gentamicin and 0.04 mg/mL dexamethasone in saline; group B, n = 30) during radiotherapy. Both mouthwashes were used 6 times daily at the onset of oral mucositis, and the treatments continued until the end of all intensity-modulated radiotherapy sessions. Oral mucositis was graded according to the Radiation Therapy Oncology Group acute radiation morbidity scoring criteria. A visual analog scale was used to assess peak mouth pain once a week, and the duration of oral mucositis was recorded.

Results. In comparison with group B, the patients in group A had a significantly lower incidence of oral mucositis of grade 3 or above (38.2% vs 66.7%, $p < 0.05$) and less peak mucosal pain in the 5th, 6th and 7th weeks of radiotherapy ($p < 0.05$). group A patients also had shorter durations of oral mucositis (35.1 days vs 39.4 days, $p < 0.05$) and lower peak swallowing function scores ($p < 0.05$).

Conclusions. The rhG-CSF mouthwash may be more effective than the compounded mouth rinse in preventing and treating radiotherapy-induced mucositis and mucositis-related pain, and thus improving the quality of life for locally advanced NPC patients. These effects should be further investigated in a prospective controlled study.

Key words: recombinant human granulocyte colony-stimulating factor, oral mucositis, radiotherapy, locally advanced nasopharyngeal carcinoma

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Nasopharyngeal carcinoma (NPC) is the most common malignant tumor of the head and neck, and radiotherapy is the main radical treatment.¹ However, radiotherapy may lead to complications, such as acute oral mucositis, especially in locally advanced NPC patients. Oral mucositis results from injury to the epithelial cells that line the oral cavity. This damage causes changes that range from mild atrophy to severe ulceration, and these symptoms are aggravated with the accumulation of the radiation dose. Serious consequences include pain requiring opioid analgesia, potentially life-threatening infections, inadequate nutrition requiring parenteral feeding, and prolonged hospitalization.^{2,3} Currently, no standard therapy prevents or treats severe oral mucositis.⁴ Most patients are treated with a topical mouth rinse containing vitamin B12.⁵

Recombinant human granulocyte colony-stimulating factor (rhG-CSF) is a hematopoietic growth factor that promotes the proliferation and differentiation of neutrophils.⁶ It has been widely used to increase the neutrophil count in patients with advanced neoplasms and to reduce the magnitude of chemotherapy-induced neutropenia.^{7,8} Another hematopoietic growth factor, human granulocyte-macrophage colony-stimulating factor (GM-CSF), has been shown to prevent and treat chemotherapy- and radiation therapy-induced oral mucositis in patients with head and neck cancer.^{9,10} However, information is lacking about the effect of rhG-CSF on radiotherapy-induced oral mucositis in locally advanced NPC patients. The present randomized controlled study was designed to observe the effects of rhG-CSF mouthwash on oral mucositis in locally advanced NPC patients.

Material and methods

Patient selection and characteristics

Patients who met the following criteria were eligible for the study: 1) age 18 or over; 2) histologically proven nasopharyngeal squamous cell carcinoma (clinical stage III or IV); 3) Karnofsky performance status > 70; 4) normal complete blood counts, liver function tests, renal function tests and blood sugar tests; 5) no history of prior radiation therapy or cytotoxic chemotherapy; and 6) no autoimmune disease.

A total of 64 patients were enrolled from January 2012 to December 2013 at the Department of Oncology at the First Affiliated Hospital of Yangtze University (Jingzhou, China). Informed consent was obtained from all the patients. There were 22 female patients and 42 male patients, and the median age was 48 years (range: 32–70 years). According to the American Joint Committee on Cancer (AJCC) 7th edition staging system, 35 patients had stage III malignancies and 29 patients had stage IV malignancies. Twenty-six of the patients were tobacco users. The patients' characteristics are shown in Table 1.

All the patients were treated with definitive radiotherapy. Cisplatin (30 mg/m²) was administered weekly for 6 weeks as a radiosensitizer. Intensity-modulated radiotherapy was adopted using 6 MV photons generated from a linear accelerator. The prescribed median doses were 73.92 Gy in 33 fractions for gross tumor volume, 69.96 Gy in 33 fractions for the positive lymph node, 60.06 Gy in 33 fractions for the high-risk clinical target volume, and 50.96 Gy in 28 fractions for the low-risk clinical target volume. The dose constraints of the organs at risk were determined in accordance with the Radiation Therapy Oncology Group (RTOG) 0615 protocol.

In addition, all the patients underwent dental prophylaxis in the form of scaling and fluoride application, and dental cavity filling and extraction were performed prior to radiotherapy. Patients with artificial dentures were advised not to wear them during the procedures. Dentists verified that none of the patients had developed oral mucositis prior to radiotherapy. The patients were counseled against using phenol- or alcohol-containing mouthwashes, tobacco, alcoholic beverages, very hot food, very cold food or spicy food. No intraoral tumor ablative procedures that altered the mucosal surfaces were carried out.¹¹ All the procedures were performed in accordance with the hospital's ethical guidelines.

Administration of rhG-CSF

The patients were randomly assigned to group A or group B. Group A patients were treated with the rhG-CSF mouthwash (saline containing 2 µg/mL rhG-CSF; QILU Pharmaceuticals, Jinan, China) at the onset of oral mucositis. Group B patients were treated with a compounded mouth rinse (saline containing 10 µg/mL vitamin B12, 0.48 mg/mL gentamicin and 0.04 mg/mL dexamethasone). Both of the oral rinses were used 6 times daily until the end of all the radiotherapy sessions. During each use, the rhG-CSF mouthwash or compounded mouth rinse was kept in the oral cavity for 3 min.

Oral mucositis was graded according to RTOG acute radiation morbidity scoring criteria. The nurses in charge of the study patients examined their oral cavities daily as part of each morning's routine care from the start of radiotherapy until all the radiotherapy sessions were over. Mouth pain was assessed using a visual analog scale (VAS) once a week during radiotherapy, and the peak mouth pain score was recorded. The duration of oral mucositis was calculated from the onset of oral mucositis to recovery. Peak swallowing problems were self-reported by patients and determined using a VAS of 0–5.¹²

Statistics

The χ^2 test and Student's t-test were used to analyze the data. SPSS Statistics 17.0 software (SPSS Inc., Chicago, USA) was used. A p-value < 0.05 was defined as statistically significant.

Table 1. Characteristics of patients with locally advanced nasopharyngeal carcinoma

Characteristics	Group A	Group B
Number of patients	34	30
Gender: number (%)		
male	22 (64.7%)	20 (66.7%)
female	12 (35.3%)	10 (33.3%)
age: mean (range)	48.6 (35–70)	47.3 (32–68)
Karnofsky performance status: number (%)		
> 80	30 (88.2%)	27 (90%)
= 80	4 (11.8%)	3 (10%)
NPC stage: number (%)		
III	19 (55.9%)	16 (53.3%)
IV	15 (44.1%)	14 (46.7%)

Table 2. The effect of rhG-CSF mouthwash on radiotherapy-induced oral mucositis in locally advanced nasopharyngeal carcinoma patients

Group	Number of patients	Grade of oral mucositis	
		1–2	3–4
A	34	21 (61.8%)	13 (38.2%)*
B	30	10 (33.3%)	20 (66.7%)

* $p = 0.02$ vs Group B; χ^2 test.

Results

The patients' characteristics are shown in Table 1. All the patients completed the radiotherapy procedure. Group A had 34 patients and group B had 30 patients. The majority of patients in both groups had Karnofsky performance status scores that were greater than 80. There was no obvious heterogeneity between characteristics of the 2 groups.

The rhG-CSF mouthwash decreased the incidence of severe radiotherapy-induced oral mucositis. More than 80% of the patients suffered from oral mucositis when the radiation dose was increased to 20 Gy. Administration of the rhG-CSF mouthwash improved oral mucositis. In comparison with group B, the incidence of oral mucositis of grade 3–4 significantly decreased in group A ($p < 0.05$, Table 2). Oral mucositis of grade 3–4 was observed in 38.2% and 66.7% of patients in group A and group B, respectively. One patient in group A and 4 patients in group B had severe oral mucositis of grade 4, and these patients received antibiotics for local infections. Good tolerance to radiotherapy was observed in 61.8% of patients with oral mucositis of grade 1–2 in group A.

The rhG-CSF mouthwash decreased the severity of radiotherapy-induced mouth pain. Mouth pain was gradually aggravated with the accumulation of the radiation dose. The most severe pain occurred in the 5th and 6th weeks of radiotherapy. Eighty-six percent of the patients used painkillers in accordance with the World Health

Organization three-step analgesic ladder principle. At each time point, the peak pain score was recorded prior to painkiller use. Compared with group B, the pain scores of the patients in group A were decreased in the 5th, 6th and 7th weeks of radiotherapy (Fig. 1, $p < 0.05$). Therefore, treatment with the rhG-CSF mouthwash decreased the incidence and severity of mucositis and improved pain relief in the mouth.

The rhG-CSF mouthwash shortened the duration of radiotherapy-induced oral mucositis. As shown in Fig. 2, the mean durations of oral mucositis

were 35.1 days and 39.4 days in group A and group B, respectively ($p < 0.05$). This suggests that the rhG-CSF mouthwash can shorten the duration of radiotherapy-induced oral mucositis and promote recovery from oral mucositis.

The rhG-CSF mouthwash improved radiotherapy-induced swallowing function scores. All the patients had different degrees of decline in swallow function. One patient in group B (but none in group A) required total parenteral nutrition. Compared with group B, the peak mean swallowing function scores in group A were significantly improved (Fig. 3, $p < 0.05$).

Side effects of the rhG-CSF mouthwash

No side effects such as nausea and vomiting were observed with the rhG-CSF mouthwash. All the patients completed the treatment.

Fig. 1. The effect of rhG-CSF mouthwash on mouth pain scores of locally advanced nasopharyngeal carcinoma patients during radiotherapy, as assessed with a visual analog scale. Group A patients received the rhG-CSF mouthwash treatment, and group B patients received a compounded mouth rinse treatment. Results are mean $\pm$ standard deviation (SD)

Fig. 2. The effect of rhG-CSF mouthwash on the duration of radiotherapy-induced oral mucositis in locally advanced nasopharyngeal carcinoma patients. Group A patients received the rhG-CSF mouthwash treatment, and group B patients received a compounded mouth rinse treatment. Results are mean $\pm$ SD

Fig. 3. The effect of the rhG-CSF mouthwash on peak mean swallowing function scores that were induced by radiotherapy in locally advanced nasopharyngeal carcinoma patients. Group A patients received the rhG-CSF mouthwash treatment, and group B patients received a compounded mouth rinse treatment. Results are mean $\pm$ SD

Discussion

Radiation inevitably injures normal tissues around the tumor in NPC patients. In particular, oral mucosal epithelial cells are extremely sensitive to radiation, and acute oral mucositis is a common complication of radiotherapy for NPC.¹³ The incidence of acute oral mucositis of grade 3–4 is 85% in radiotherapy patients with advanced NPC.² This complication seriously affects the patients' quality of life and nutrition status. Oral mucositis can increase the potential risk of oral infection, which could result in suspension of radiotherapy and a poor curative effect.¹⁴

In this study, topical application of rhG-CSF mouthwash was demonstrated to be effective for the prevention and treatment of radiotherapy-induced oral mucositis in locally advanced NPC patients. Significant decreases in the duration and severity of oral mucositis, reductions in the degree of pain and improvements in swallowing function

were attributed to the effects of the rhG-CSF mouthwash. The control group received a standard compounded mouth rinse that has been used in the authors' department with good results. The compounded mouth rinse was also effective against oral mucositis.

Importantly, rhG-CSF is a 19.6-kDa glycoprotein that is characterized as a growth factor for hematopoietic progenitor cells.¹⁵ It has been approved by the US Food and Drug Administration and the European Medicines Agency (EMA), and is commonly used to treat neutropenia and to mobilize bone marrow hematopoietic stem cells for transplantation.¹⁶ A previous study showed that GM-CSF influences the proliferation and differentiation of stem cells and regulates several functions in mature leukocytes, macrophages and dendritic cells in the mucosa and dermis.^{17,18} Therefore, the present authors speculated that the potential mechanism of the effects of rhG-CSF on oral mucositis was associated with the proliferation and differentiation of mucosal stem cells.

In summary, the topical application of rhG-CSF effectively prevented and treated radiotherapy-induced oral mucositis in locally advanced NPC patients. Furthermore, treatment with rhG-CSF improved the quality of life for these patients without inducing any side effects. Therefore, these effects should be further investigated in a prospective, controlled study.

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