[Original Research]

Irsogladine Maleate Reduces Radiotherapy or Chemoradiotherapy Oral Mucositis in Patients with Head and Neck Cancer

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Abstract: To investigate the effect of irsogladine on radiotherapy-induced oral mucositis, a prospective randomized study of 43 patients (10 female, 33 male) with head and neck cancer was conducted from November 2010 to December 2011. Group A (n = 21) received irsogladine 4 mg/day during radiotherapy and Group B (n = 22) received radiotherapy without irsogladine. Oral Mucositis Weekly Questionnaire—Head and Neck Cancer (OMWQ-HN), Revised Oral Assessment Guide (ROAG), Numeric Rating Scale (NRS) and Common Terminology Criteria for Adverse Events (CTCAE) scores were analyzed by the Mann-Whitney U-test. Quality of life measured by OMWQ-HN gradually declined in both groups. However, the score for Group A was significantly higher than that for Group B at 50 Gy of radiotherapy. A significant increase in ROAG score was observed in both groups, but the score for Group A was significantly lower than that for Group B after 20 Gy. There was no difference in safety score between the two groups as measured by CTCAE ver. 4. In conclusion, it was found that irsogladine reduced oral mucositis lesions associated with radiotherapy in patients with head and neck cancer.

Key words: irsogladine, radiotherapy, head and neck cancer, mucositis

INTRODUCTION

Radiotherapy is one of the effective treatment strategies for head and neck cancer.[1, 2] However, it has the adverse effect of oral mucositis accompanied by painful mucosal ulceration which causes xerostomia and dysphagia.[3] Consequently, radiotherapy results in dehydration, malnutrition, and weight loss.[4] The causes of radiotherapy-induced oral mucositis are the cytotoxic action of radiation on oral mucosa and infection due to the immunosuppressive effect of the radiation.[5] Currently, there is no Food and Drug Administration-approved cytoprotective agent that reliably prevents radiotherapy-induced mucositis for head and neck cancer. Therefore, agents effective for such lesions are strongly desired to improve patients' quality of life.

Irsogladine (2,4-diamino-6-[2,5-dichlorophenyl]-*s*-triazine maleate), an anti-ulcer drug widely used in Japan, Korea, and China, protects the gastric mucosa from ulceration by enhancing the mucosal defense mechanism through the facilitation of gap-junctional intercellular communication.[6, 7] Irsogladine is absorbed in the small intestine and distributed in the entire gastrointestinal tract.[8] It heals oral aphthae more rapidly than spontaneous healing in patients with either relapsing aphthous stomatitis or Behçet disease by oral administration.[9] It also prevents the development of methotrexate-induced aphthous stomatitis in patients with rheumatoid arthritis.[10] Furthermore, a placebo controlled double-blinded study showed that irsogladine maleate reduced the incidence of fluorouracil-based chemotherapy-induced oral mucositis.[11] In addition, successive administration of irsogladine following 10 Gy of irradiation increases the survival of mouse intestinal stem cells in a dose-dependent manner.[12] On the basis of these findings, we hypothesized that irsogladine maleate might be useful for the palliation of radiotherapy-induced mucositis. In the present study, we investigated the preventive effect of irsogladine on oral mucositis associated with radiotherapy in patients with head and neck cancer.

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PATIENTS AND METHODS

1. Patients

Subjects were patients with head and neck cancer who underwent radiotherapy at Fukuoka University Hospital between November 2010 and December 2011. The study was approved by the ethics committee of Fukuoka University Hospital (number: 10-078) and written informed consent was obtained from all patients. The inclusion criteria were: 1) age 20 or older and age 80 or

younger, 2) a planned radiation dose of 30 Gy or more, and 3) no signs of complicated gastritis. The exclusion criteria were: 1) the continuous use of any of the following drugs or substances within 1 week before the beginning of the study: gastric mucosal protective drugs, edaravone, vitamin B, oral azulene sulfonate tablets, oral steroid preparations, oral povidone iodine preparations, oral antibiotic preparations, tranexamic acid, glycyrrhetic acid, traditional Chinese herbal medicines, hydrogen peroxide gargle, aluminum potassium sulfate gargle, or local anesthetic gargle (however, vitamin B, tranexamic acid, glycyrrhizinate and traditional Chinese herbal medicines were permitted if they were administered 2 weeks or more before the start of radiotherapy), 2) symptoms of mucositis-like conditions such as lichen planus or pemphigus or the presence of Behçet disease, 3) the presence of another cancer besides head and neck cancer, 4) a performance status of 4, and 5) any other concomitant condition or circumstance judged to make the subject ineligible for participation in the study. In this study, not only the patients who took both chemotherapy such as S1, TPF (docetaxel, cisplatin, 5-fluorouracil), superselective intraarterial infusion cisplatin or CF (cisplatin, 5-fluorouracil) and radiotherapy but also the patients who took only radiotherapy were included as the subjects.

2. Study design and treatments

This was a prospective, randomized study. The patients were randomly assigned to Group A to receive azunol gargle and oral irsogladine 4 mg daily during radiotherapy or Group B to receive azunol gargle without irsogladine during radiotherapy (Fig. 1a). Because there are no other studies which show that irsogladine reduces radiotherapy-induced mucositis, this was considered an exploratory trial. Therefore, taking into account feasibility considerations, we decided to enrol 20 patients in each group. In Group A, irsogladine was orally administered for a period of 1 week before the start of radiotherapy. In this study, we determined to confirm the efficacy of irsogladine by focusing on its main mechanism, that is, the activation of gap junctional intercellular communication. Irsogladine increases cell coupling in rabbit gastric epithelial cells in a concentration-dependent manner from 10^{-6} M. To achieve this concentration, patients must take irsogladine for at least 7 days.[13] This is why we administered irsogladine from 1 week before the start of radiotherapy in Group A. Azulene (Azunol® Gargle liquid 4%, Nippon Shinyaku Co., Kyoto, Japan) was used to prepare azulene oral rinse by adding seven drops of the 4% liquid solution to 100 ml water. At the start of radiotherapy, patients performed an oral rinse with azulene solution 4–6 times a day and continued to do this until the end of radiotherapy. According to European Society for Medical Oncology, frequent use of non-medicated oral rinses (e.g. saline mouth rinses 4–6 times/day) is recommended.[14] Moreover, on the basis of the Multinational Association of Supportive Care in Cancer guidelines, benzydamine is recommended for prevention of radiotherapy-induced mucosits.[15] However, in Japan benzydamine is not approved by the Health, Labour and Welfare Ministry. On the other hand, gargling with sodium azulene sulfonate which has anti-inflammatory effect, such as leukocyte migration inhibition or histamine release suppression,[16] is commonly used for the treatment and prevention of mucositis induced by various factors. Therefore, we determined to use the gargling with sodium azulene sulfonate as the basic remedy in this trial.

The radiation fields for nasopharyngeal and primary unknown cancers extended from the nasopharynx to the infraclavicular region. The radiation treatment of mesopharyngeal and hypopharyngeal cancer was carried out by a shrinking field technique in which the initial fields included the total neck from the nasopharynx to the supraclavicular nodal region and the boost fields included the primary tumor and neck nodal metastases. The radiation fields for laryngeal cancer included the larynx, hypopharynx and whole neck. The radiation fields for oral cavity cancer included the oral cavity, oropharyngeal and upper region of hypopharynx and neck. The radiation fields for submandibular gland cancer extended from the submandibular gland to the upper region of the clavicle. Although the radiation field depends on the type of cancer and the presence or absence of metastasis, radiotherapy-induced mucositis develops during the treatment of any type of head and neck cancer.[17]

The Oral Mucositis Weekly Questionnaire—Head and Neck Cancer (OMWQ-HN),[18] the Revised Oral Assessment Guide (ROAG),[19, 20] and the Numeric Rating Scale (NRS) were used for evaluation. ROAG, a tool for evaluating oral health status and oral function, is a scoring

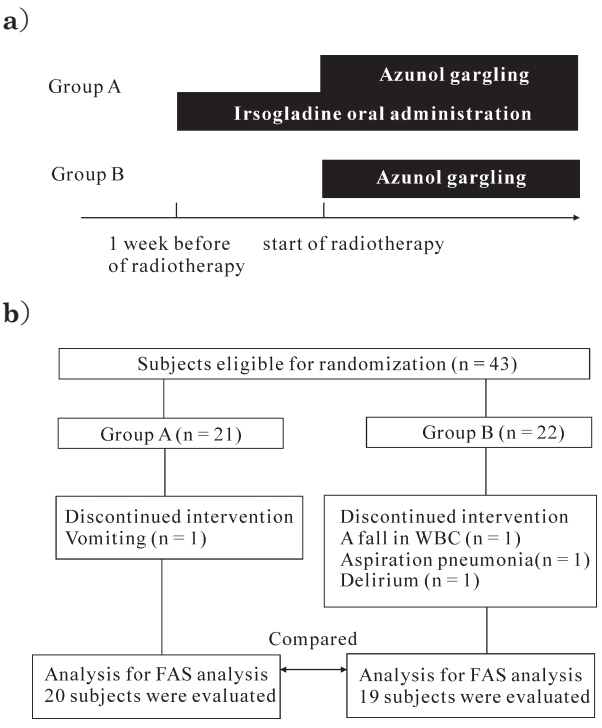

Fig. 1 a) Study design, b) Flow chart of study subjects.

system of eight categories comprising voice, swallowing, color and dryness of lips and tongue, saliva, color and state of mucous membranes, gingiva and teeth. The score ranges from 1 (normal) to 3 (moderate-to-severe change). The ROAG score was assessed before radiotherapy and at cumulative doses of 10, 20, 30, 40 and 50 Gy of radiotherapy. Side effects were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.[21] The evaluation by ROAG was done by ENT doctors along with pharmacists. The evaluation of oral mucositis was included in the items of ROAG. This evaluation was done before meals to avoid the vias of the dryness of the mouth. The primary endpoint is the preventive efficacy of irsogladine for radiotherapy-induced mucositis, and the secondary endpoint was the evaluation by ROAG, pain control, and safety of irsogladine.

3. Statistical analysis

The subjects were randomly assigned to the two groups by using random numbers generated by SAS (SAS Institute, Cary, NC, USA). For continuous or categorical variables, the statistical significance of differences between groups was determined with the *t*-test or Wilcoxon rank-sum test, and the statistical significance of differences within a group was determined with the Wilcoxon signed-rank test. For binary variables, the statistical significance of differences between groups was determined with the χ^2 test. All reported p values are two-sided, and $p<0.05$ was considered to be statistically significant. Statistical analyses were performed with SAS ver. 9.2 (SPSS, Chicago, IL, USA), Windows edition.

RESULTS

Forty-three patients (10 female, 33 male) were enrolled in the study. Of these 43 patients, four were ineligible because they could not continue with radiotherapy due to vomiting, a fall in white blood cell count, aspiration pneumonia, or delirium in Full-analysis-set (FAS) as shown in Fig. 1b. There was no significant difference between the groups in age, gender, concomitant chemotherapy, cancer type, or cancer stage (Table 1). There were 20 Group A and 19 Group B patients. Patients in both groups received at least 30 Gy irradiation, although the cumulative amount differed among the patients (Table 2).

The OMWQ-HN score from 0 to 40 Gy of radiotherapy did not differ significantly between the groups. However, at 50 Gy of radiotherapy, the score for Group A was significantly higher than for Group B (Group A, 8.3±2.5; Group B, 6.3±2.7; $p=0.031$). When the cumulative dose of irradiation was 20 Gy or more, the total ROAG score for Group A was significantly lower than for Group B (Fig. 2). Significant diferrences between the two groups were observed in the ROAG scores for the lips, mucous

Table 1 Baseline and disease characteristics and treated patients

	Group A ($n=20$)	Group B ($n=19$)	p-value
Gender			
Female	6	3	*N.S.*
Male	14	16	
Age, years			
Mean ± *S.D.*	66.9 ± 7.6	66.9 ± 7.6	*N.S.*
Range	51–79	49–78	
Concomitant chemotherapy			
S1	13	12	
TPF	1	2	
S-CDDP	1	0	*N.S.*
CF	0	2	
None	5	3	
Cancer type			
Nasopharyngeal	1	0	
Mesopharyngeal	8	5	
Hypopharyngeal	3	5	
Laryngeal	4	4	*N.S.*
Oral cavity	4	1	
Submandibular gland	0	2	
Primary unknown	0	2	
Cancer stage			
I	2	3	
II	10	6	*N.S.*
III	1	3	
IV	7	7	

TPF: docetaxel, cisplatin, 5-fluorouracil. S-CDDP: superselective intraarterial infusion cisplatin. CF: cisplatin, 5-fluorouracil.
N.S.: no significant difference between groups.
There is no definite regimen for each stage of cancer. The therapeutic method was determined according to patients' condition by doctors.

Table 2 The number of cases who completed each accumulative irradiation

Group	Accumulative irradiation (Gy)					
	0	10	20	30	40	50
A	20	20	20	20	16	12
B	19	19	19	19	10	10

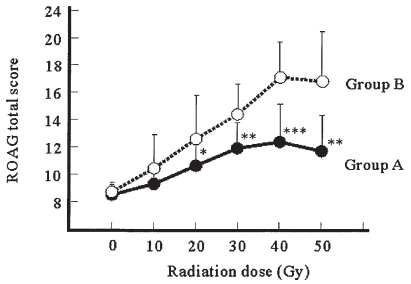

Fig. 2 Transition of the Score of ROAG.

membrane, tongue and saliva at a cumulative dose of 50 Gy (Table 3). The mean NRS score for Group A was significantly lower than for Group B at 40 Gy of radiotherapy ($p=0.031$) (Fig. 3). No significant differences in CTCAE scores were observed between the groups (Table 4). Additionally, no side effects, such as rash or itching, were observed in any of the patients.

DISCUSSION

In the present study, the use of irsogladine maleate before and during radiotherapy for head and neck cancer reduced radiation-induced oral mucositis. In previous studies, other drugs showed efficacy in the prevention of radiotherapy-induced mucositis. Thus, benzydamine is recommended for the prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy[15] by the Clinical Practice Guidelines for the Prevention and Treatment of Mucositis reported by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer, the International Association of Supportive Care in Cancer, and the International Society for Oral Oncology. A randomized placebo-controlled trial in patients with head and neck cancer has shown that oral rinse with benzydamine reduces radiation-induced erythema and ulceration by 30%.[22] Polaprezinc is reported to be effective for the prevention of oral mucositis induced by radiation or radiochemotherapy when patients perform an oral rinse with polaprezinc solution for 3 min four times a day.[23] In contrast to oral rinses, which should be used several times a day, irsogladine is effective by oral administration once a day. For this reason, irsogladine has an advantage in compliance.

Some studies indicate that radiation-induced mucositis is associated with the presence of free radicals.[24, 25] Irsogladine suppresses the production of superoxide anion (O_2^-) in a concentration-dependent manner by

Table 3 Analysis of oral status of Groups A and B at 50 Gy by ROAG

ROAG category	Grade	Group A ($n=12$)	Group B ($n=10$)	p-value
Voice	1	10	2	0.032
	2	2	7	
	3	0	1	
	4	0	0	
Swallowing	1	3	0	*N.S.*
	2	9	9	
	3	0	1	
	4	0	0	
Lips	1	10	2	0.002
	2	2	7	
	3	0	1	
	4	0	0	
Teeth	1	9	4	*N.S.*
	2	3	5	
	3	0	1	
	4	0	0	
Mucous membrane	1	5	1	0.037
	2	7	7	
	3	0	2	
	4	0	0	
Gingiva	1	10	5	*N.S.*
	2	2	3	
	3	0	2	
	4	0	0	
Tongue	1	6	1	0.022
	2	6	6	
	3	0	3	
	4	0	0	
Saliva	1	6	0	0.003
	2	6	5	
	3	0	5	
	4	0	0	

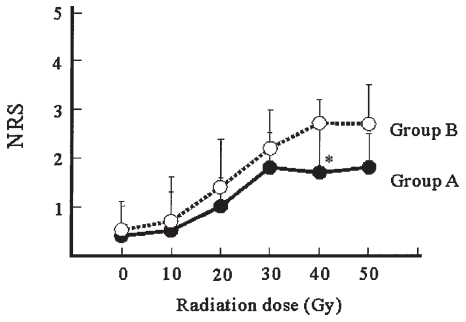

Fig. 3 Transition of the Score of NRS.

Table 4 The number of side effects in each group by CTCAE ver.4

CTCAE ver.4 category	Group A ($n=20$)	Group B ($n=19$)	p-value
Liver dysfunction	0.3 ± 0.6	0.4 ± 0.8	*N.S.*
Constipation	2.0 ± 2.6	2.4 ± 1.8	*N.S.*
Diarrhea	0.2 ± 0.5	0.3 ± 0.7	*N.S.*
Rash	0	0	*N.S.*
Itching	0	0	*N.S.*

inhibiting phosphodiesterase.[26] Inhibition occurs in a dose-dependent manner from 10^{-7} M irsogladine, a concentration that is reached in the blood about 1.5 h after a single administration.[27] Therefore, even if the oral administration of irsogladine were started at the same time as radiotherapy, it may well still have a preventive effect on radiation-induced mucositis. Further study is needed to ascertain the mechanism of action of irsogladine.

The increase in total ROAG score in the irsogladine group was significantly smaller than in the control group when the cumulative dose was 20 Gy or higher. In particular, an anti-inflammatory effect of irsogladine was observed in the mucosa, lips, and tongue. Previous studies have shown that cytokines are induced in the oral mucosa in patients developing mucositis during radiotherapy for head and neck cancer.[28] Furthermore, irsogladine maleate regulates the epithelial barrier function of human gingival epithelial cells stimulated by tumor necrosis factor-α.[29] Such anti-inflammatory effects may contribute to the suppression of radiation-induced mucositis. We have previously found that radiotherapy aggravates mucositis at doses of 20 Gy or higher. Therefore, the results obtained in the present study are relevant to the previous study. In addition, the NRS scores for the irsogladine group were significantly lower than those for the control group at 40 Gy of radiotherapy. It is not clear whether irsogladine inhibits the pain of mucositis, because we controlled the pain after the start of radiation therapy. However, we consider that the significant difference in ROAG between the groups might be attributable to pain relief in the irsogladine group. In our cilinical practice, we often experience radiation-induced mucositis which is intractable to other medical approaches. Accordingly, the clinical application of irsogladine is expected in the near future. Study limitations include small sample size and open labeled examination because this is a preliminary trial to investigate the preventive efficacy of irsogladine for radiotherapy-induced mucositis at our hospital. Therefore, multicenter trials with large numbers of patients should be carried out in a placebo controlled double-blinded study to confirm our results.

Irsogladine appears to be useful for the reduction of oral mucositis associated with radiotherapy in patients with head and neck cancer. It is expected that the use of irsogladine would lead to a great improvement in the quality of life of such patients.

Conflict of interest

All authors declare that they have no financial relationships or conflicts of interest relevant to this publication and that the work is original.

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