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Irsogladine maleate reduces the incidence of fluorouracil-based chemotherapy-induced oral mucositis

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Background: Oral mucositis is one of the most common side-effects of 5-fluorouracil (5-FU)-based chemotherapy. The objective of this study was to evaluate the effects of irsogladine maleate (IM) on fluorouracil-induced oral mucositis through a double-blind, placebo controlled trial.

Patients and methods: Patients ($N = 66$) were randomly assigned to receive either placebo or IM (4 mg/day for 14 consecutive days). The incidence and maximum severity of fluorouracil-induced oral mucositis and safety of the irsogladine dosing regimen were evaluated.

Results: A cohort of 33 patients received placebo and 33 patients received IM. The incidence of oral mucositis was significantly lower for IM than for placebo (27% versus 73%; $P < 0.001$ by chi-square test). Specific adverse events considered related to IM were not found.

Conclusion: IM significantly reduced the incidence and maximum severity of oral mucositis in patients treated with 5-FU-chemotherapy.

Key words: 5-fluorouracil, chemotherapy, irsogladine maleate, oral mucositis

introduction

Oral mucositis is one of the most common side-effects of chemotherapy. Resultant oral mucositis may be painful, temporarily interfere with oral intake and nutrition, and may become a mucosal infection, occasionally leading to systemic infection. Severe oral mucositis, which may result in dose reductions and/or delays in treatment, has the potential to affect overall survival, and is an important clinical problem. The drug 5-fluorouracil (5-FU) is the most effective and frequently used agent for treating gastrointestinal cancer, and is well known for causing mucositis.

Irsogladine maleate (IM) is known to be effective for the treatment of gastric ulcer [1] and aphthous stomatitis [2, 3]. In one report involving a small number of patients, IM reduced the incidence of transient and relapsing chemotherapy-induced oral mucositis in rheumatoid arthritis treated with methotrexate; however, it was not stated whether the investigators were blinded to the patient group assignments [3]. We hypothesized that IM, which inhibits production of proinflammatory cytokines and reinforces gap junctional intercellular communication [4–9], would be effective in reducing chemotherapy-induced oral mucositis. To the best of our knowledge, no prospective randomized clinical trial has been conducted investigating the reduction of chemotherapy-induced oral mucositis by IM in cancer patients.

The objective of the present study was to evaluate the effects of IM on fluorouracil-induced oral mucositis through a double-blinded, placebo-controlled clinical trial.

patients and methods

patients

The study was conducted from January 2012 to June 2012 at Kansai Medical University Hospital. Eligibility criteria were the following: (i) age >20 years; (ii) histological diagnosis of carcinoma; (iii) chemotherapy consisting of 5-FU and platinum; and (iv) no previous head and neck radiotherapy. Patients taking other investigational drugs such as rebamipide, allopurinol, camostat mesylate, polaprezinc, pilocarpine, cevimeline, nonsteroidal anti-inflammatory drugs, IM, teprenone, and lafutidine within 14 days of study initiation or with plans to use topical or systemic treatments for oral mucositis during the study were excluded.

Before enrollment, patients had to fully recover from the oral mucosal symptoms (i.e. achieve World Health Organization (WHO) grade 0] and have an Eastern Cooperative Oncology Group performance status of ≤2; no dental problems (i.e. carious tooth, mobility of tooth, unfitness artificial tooth); absolute neutrophil count $\geq 1.5 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l; and normal hepatic and renal function. Written informed consent was obtained from each patient before entering the study. The study protocol

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was approved by the institutional review boards of the institution and was conducted in accordance with the principles of the Declaration of Helsinki.

study design and treatment plan

The study was a prospective, randomized, double-blind, placebo-controlled, phase II trial, and eligible patients were randomly assigned in a 1:1 ratio using a permuted block method. Stratification factors included primary cancer site, chemotherapy regimen, and performance status. There were two treatment arms: arm 1, IM was administered orally twice a day, 4 mg/day; arm 2, placebo. Treatment started on the first day of cycled chemotherapy and continued daily for 14 days. IM was dissolved in normal saline solution. The placebo (normal saline solution) and test drug were identical in all respects, including color, taste, and volume, except for the presence or absence of active drug. In addition, oral rinse with sodium gualenate hydrate, as standard oral care, was also used four times daily in the two groups for study periods. Medications for oral mucositis and oral rinse containing chlorhexidine, hydrogen peroxide, or diphenhydramine were not allowed. Local anesthetic oral rinses (i.e. viscous lidocaine) were not allowed. Use of systemic opioid analgesics was permitted at the investigator's discretion. Patients received chemotherapy consisting of continuous infusion of 5-FU 800 mg/m^2/day on days 1–5 and cisplatin 80 mg/m^2 on day 1, repeated every 4 weeks, or consisted of continuous infusion of 5-FU 700 mg/m^2/day on days 1–5 and nedaplatin 130 mg/m^2 on day 6, repeated every 4 weeks.

assessments and end points

Oral mucositis was assessed according to WHO criteria (supplementary Table S1, available at *Annals of Oncology* online) [10]. By using the same schedule as oral mucositis evaluation, patients reported Mouth and Throat Soreness (MTS) score (Question 4; assessed from 0 to 10) [11]. The other adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0). Complete blood cell counts and serum biochemistry examinations were carried out weekly for the study period. Patients were assessed for adverse events including oral mucositis by an independent physician at baseline, on study days 1, 3, 5, 8, 10, 12, 14, 21, and at the end of chemotherapy cycles.

The primary end point of this study was the incidence of fluorouracil-induced oral mucositis (WHO grade ≥1). Secondary end points were the incidence of severe oral mucositis (WHO grade ≥3), MTS score, and the other adverse events according to NCI-CTCAE. All end points were analyzed for comparisons of IM versus placebo.

statistical methods

Sample size estimates were based on data from a preliminary study in 5-FU associated oral mucositis (WHO grade ≥1) in which 10 (76.9%) of 13 patients treated with placebo, and 4 (36.4%) of 11 patients who were treated with IM were observed. The number of subjects required to detect a significant difference with an α level of 0.05 (two sided) and a β level of 0.2 was 32 per group. This determination assumed an incidence of WHO grade ≥1 oral mucositis of 75% in the placebo group and 35% in the IM group, and considered the likelihood that some subjects would be excluded from the analysis.

All patient characteristics were considered categorical variables, with the exception of age, which was treated as continuous data. Specific comparisons between groups were made using chi-square and Mann–Whitney tests. To evaluate the impact of IM on the development of oral mucositis, multivariate logistic regression analysis was applied adjusting for baseline patient characteristic factors including age, smoking history, serum albumin, and stage. Statistical analyses were carried out using the SPSS statistical software package version 11 (SPSS Inc., Chicago, IL), and a P value <0.05 was considered statistically significant.

results

patient characteristics

A total of 67 patients were enrolled in the study and were randomly assigned to either the IM group or placebo group (Figure 1). One patient was excluded from analysis in the IM group due to not having completed any of the follow-up information. Thus, 66 patients were analyzed in the study. Baseline demographic and clinical characteristics were similar between treatment groups (Table 1). The median ages were 63 years (range, 35–79 years) and 62 years (range, 30–79 years) in the IM and placebo groups, respectively. Eighty-three percent of all patients had tumors in the head and neck or esophagus. Most patients had stage III–IV tumors (82%). Compliance with IM or placebo treatment was perfect; 100% of patients received the full planned dose. No patient in the study required a dose reduction of chemotherapy in the two groups. The median

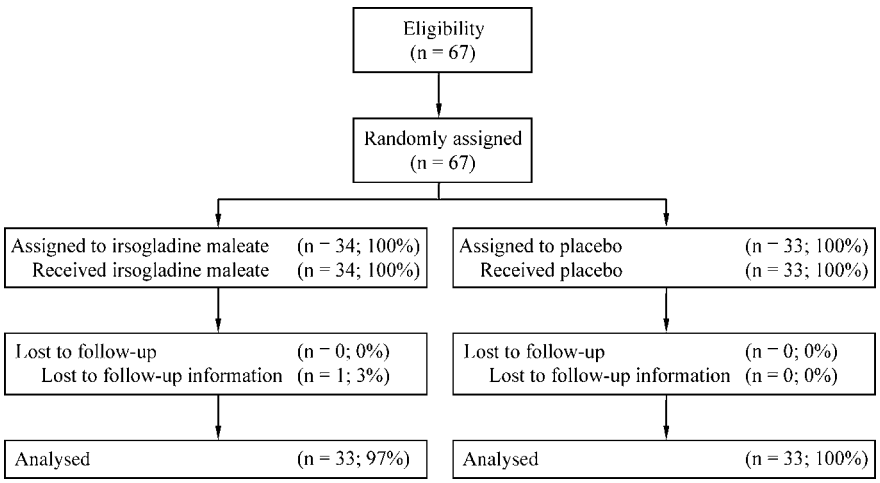

Figure 1. Study Schema.

Table 1. Demographics and clinical characteristics at baseline

	Irsogladine maleate ($N = 33$)	Placebo ($N = 33$)	P
Age (years)			
Median	63	62	0.45
Range	35–79	30–79	
Gender			
Male	20	21	0.8
Female	13	12	
Performance status			
0	14	15	0.97
1	15	14	
2	4	4	
Smoking history			
Never	19	14	0.22
Former	14	19	
Brinkman index			
Median	730	780	0.42
Range	0–2400	0–3360	
Serum albumin (g/dl)			
Median	3.8	3.7	0.35
Range	2.3–4.8	2.5–4.7	
Pathology			
Squamous cell carcinoma	33	33	–
Cancer site			
Head and neck	16	15	0.99
Oral cavity	2	3	
Nasal cavity	0	1	
Oropharynx	6	4	
Hypopharynx	8	7	
Esophagus	11	13	
Lung	1	1	
Cervical	4	3	
Unknown primary site	1	1	
Stage			
I	0	1	0.84
II	2	1	
III	7	7	
IV	21	19	
X	3	5	
Recurrence	2	4	
Unknown primary site	1	1	
Opioid use			
Yes	5	5	1
No	28	28	
Chemotherapy regimen			
5-FU–cisplatin	9	6	0.38
5-FU–nedaplatin	24	27	

total 5-FU doses were 3500 mg (range, 3500–4000 mg) in each group ($P = 0.38$). Five patients with cancer pain require the use of opioid before enrollment in each group. No patient used other pain medication than opioid. The median opioid doses (in orally morphine equivalents) were 20 mg/day (range, 15–30 mg/day) and 32.4 mg/day (range, 18–36 mg/day) in the IM and placebo groups, respectively ($P = 0.40$). During the study period, none of the patients increased opioid doses.

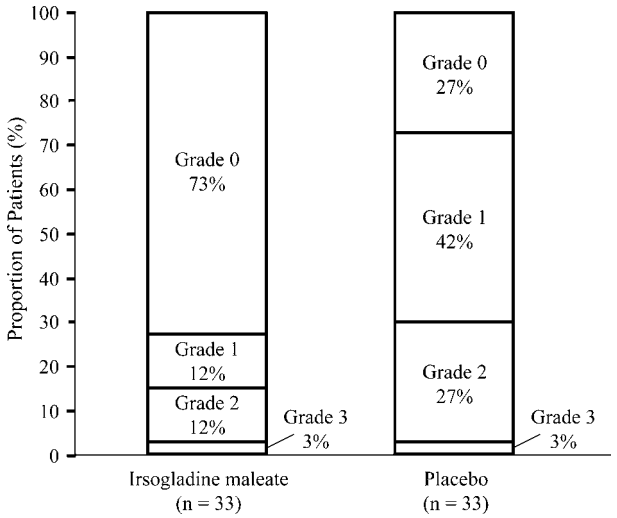

Figure 2. The maximum severity of oral mucositis according to WHO criteria.

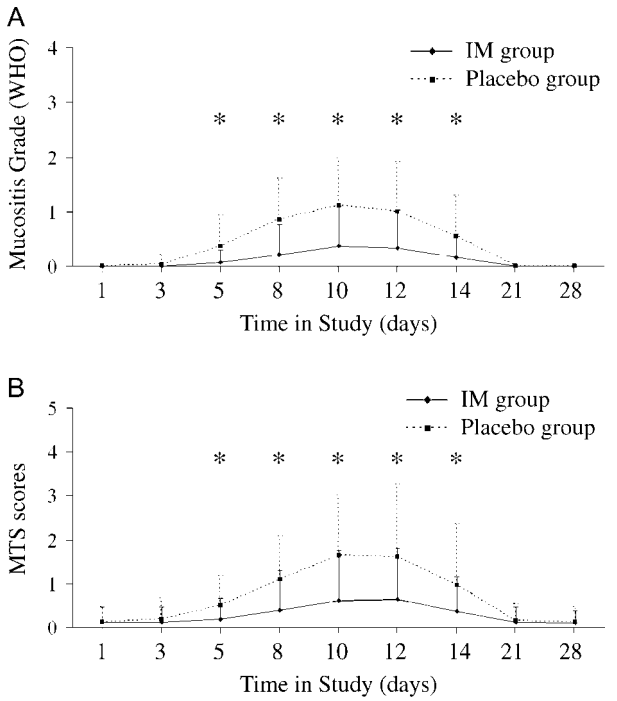

Figure 3. The mean scores changing in oral mucositis according to WHO criteria (A) and Mouth and Throat Soreness (MTS) score (Question 4; assessed from 0 to 10) (B). Error bars represent standard deviations of measurements. *There were significant differences between the two groups.

efficacy and toxicity

The incidence and maximum severity of oral mucositis according to WHO criteria are summarized in Figure 2. The primary end point, the incidence of oral mucositis (WHO grade ≥1), was 27.3% in the IM group and 72.7% in the placebo group [hazard ratio 0.14, 95% confidence interval (CI) 0.05–0.42, $P < 0.001$ by chi-square test]. No patient experienced grade 4 oral mucositis. With multiplicity adjustment, there was

Table 2. Toxicity

	Irsogladine maleate ($N = 33$)					Placebo ($N = 33$)					P^*
	Grade					Grade					
	1	2	3	4	≥3 (%)	1	2	3	4	≥3 (%)	
Leukopenia	2	13	6	3	27	7	7	8	3	33	0.59
Neutropenia	2	5	5	5	30	4	5	5	4	27	0.78
Anemia	14	9	6	0	18	15	11	5	0	15	0.74
Thrombocytopenia	20	4	2	3	15	12	5	4	4	24	0.35
Diarrhea	6	0	0	0	0	6	0	0	0	0	1.0
Vomiting	3	0	0	0	0	1	0	0	0	0	1.0
Nausea	12	3	0	–	0	12	0	1	0	3	0.31
Fatigue	8	2	0	–	0	6	1	0	0	0	1.0
Febrile neutropenia	–	–	2	0	6	–	–	2	0	6	1.0

a significant difference in the incidence of oral mucositis between the two groups (hazard ratio 0.05, 95% CI 0.009–0.27, $P < 0.001$ by multivariate logistic regression analysis). By multivariate analysis, no baseline patient characteristic factor was significantly associated with the development of oral mucositis ($P > 0.05$). The changes in oral mucositis according to WHO criteria (Figure 3A) and MTS score (Figure 3B) are presented in Figures 3. The both scores on study days 5, 8, 10, 12, and 14 were significantly lower in the IM group than in the placebo group (all $P < 0.05$) (Figure 3). The secondary end point, the incidence of severe oral mucositis (WHO grade ≥3), was one patient in each group ($P > 0.05$). Most patients (98%) experienced at least one adverse event. Only one patient receiving placebo did not experience an adverse event. The incidence of adverse events was similar between the two groups (Table 2).

Grade 3 or higher adverse events occurred in the IM and placebo groups, respectively, and included leucopenia (27% and 33%), neutropenia (30% and 27%), anemia (18% and 15%), thrombocytopenia (15% and 24%), nausea (0% and 3%), and febrile neutropenia (6% and 6%). None of these events led to study withdrawal. There were no other notable laboratory changes and no treatment-related deaths in either group. Specific adverse events considered related to IM were not found.

discussion

Our findings indicate that IM can significantly reduce the incidence of oral mucositis in patients receiving fluorouracil-based chemotherapy when compared with placebo. There were two schedules of 5-FU. It has been reported that hematologic toxicity was less frequent with continuous infusion 5-FU than with bolus 5-FU [12, 13]. However, the risks of severe diarrhea, nausea/vomiting and mucositis were not different in the continuous infusion 5-FU and bolus 5-FU. The incidence of mucositis was similar in both administration schedules (9% with continuous infusion 5-FU and 7% with bolus 5-FU). To date, only cryotherapy is recommended by the Multinational Association of Supportive Care in Cancer guidelines before bolus doses of 5-FU administration [14]. Although cryotherapy is useful for short bolus chemotherapeutic infusions, based on the hypothesized mechanism, cryotherapy may not work in patients receiving continuous intravenous chemotherapeutic infusions. Recently, some reports are available on keratinocyte growth factor (palifermin) reducing the incidence of chemotherapy- or chemoradiotherapy-induced mucositis [15–17]. Our results showed that IM significantly reduced in the incidence of 5-FU-induced oral mucositis and had an efficacy similar to that of palifermin [15]. In this study, specific adverse events caused by IM were not found, although palifermin has been reported to cause oral-related adverse events and increases in serum amylase and lipase [15–17].

The mechanism of chemotherapy-induced mucositis has been described through a sequence of events [18]. First, chemotherapy causes direct DNA damage resulting in the death of basal epithelial cells and the generation of reactive oxygen species (ROS) that damage connective tissue, DNA, and cell membranes. Second, this cell damage causes the activation of several transcription factors including nuclear factor-kappa B (NF-κB), wnt, and p53, and their molecular pathways. Third, these pathways are further amplified via positive feedback loops. For example, tumor necrosis factor-α (TNF-α) is a potent activator of NF-κB upregulating TNF-α expression, resulting in increased expression of NF-κB and TNF-α. TNF-α is also a potent activator of sphingomyelinase leading to the production of ceramide that results in stimulation of apoptosis. Finally, cell death causes mucosal thinning, resulting in the development of clinical and symptomatic ulcerated mucositis.

IM produces the increase of intracellular cyclic adenosine monophosphate (cAMP), and inhibits the ROS production in neutrophils by the increase of cAMP content by phosphodiesterase type 4 (PDE4) inhibition [4, 5]. The inhibition of the ROS production in neutrophils may result in the reduction of chemotherapy and/or radiotherapy-induced damage. However, there is no report that IM has the action of ROS scavenger. The proinflammatory cytokine TNF-α is a necessary factor in the chain of pathophysiological events leading to inflammation. IM inhibits TNF-α release through the inhabitation of PDE4 [6]. IM also inhibits the production of proinflammatory cytokines including IL-1B and IL-8, and protects the mucosal cells [7, 8]. Furthermore, IM has the therapeutic actions by maintaining the homeostasis of mucosal cells, by reinforcing gap junctions, and accelerating intercellular communication in the oral and gastric mucosa [9]. It seems that all of these effective functions may cause the reduction of chemotherapy-induced oral mucositis.

The severity of the neutropenia has been associated with the incidence and severity of chemotherapy-induced oral mucositis [19]. Grade 3 or higher adverse events in this study were mostly chemotherapy-induced myelosuppression, included leucopenia, neutropenia, and febrile neutropenia. The main adverse events of chemotherapy consisting of 5-FU and nedaplatin were myelosuppression, and similar adverse events were previously observed [20]. There were no significant differences between treatment groups in the incidence and severity of adverse events.

A potential weakness of the study is that all study patients with squamous cell carcinoma were Asian. This was a single institution study with a small number of patients. Therefore, for validation, additional prospective, multicenter phase III studies with large numbers of patients with adenocarcinoma or squamous cell carcinoma are needed.

In conclusion, IM significantly reduced the incidence of oral mucositis in patients treated with 5-FU chemotherapy. Our study adds to the evidence suggesting that IM is useful in prevention of oral mucositis.

disclosure

The authors have declared no conflict of interest, financial interests, funding considerations, or sources of study support.

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