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The Elental® elemental diet for chemoradiotherapy-induced oral mucositis: A prospective study in patients with oral squamous cell carcinoma

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Abstract. Oral mucositis is a common adverse effect of cancer treatment that can increase the risk for local and systemic infection. This prospective study was designed to evaluate the preventive effects of an amino-acid-rich elemental diet (ED), Elental®, on radiotherapy- or chemoradiotherapy-induced mucositis in oral squamous cell carcinoma (OSCC) patients. Fifty patients were enrolled in this prospective study, who had received radiation (60-70 Gy) with/without chemotherapy [S-1, UFT, cisplatin (CDDP), docetaxel (DOC) plus CDDP, or Cetuximab]. The Elental® group (25 patients) had received Elental® during treatment, and the control group (25 patients) had not. Multivariate logistic regression analysis was used to identify the factors related to abatement of oral mucositis. A comparison of the rates of completion of chemoradiation treatments as well as the nutritional or inflammatory status between Elental® and control groups was performed. Multivariate analysis indicated that most of the patients who received Elental® suffered from a lower degree of mucositis and showed significantly improved rate of completion of chemoradiation (no interruption) compared to the control group. There was a significant difference between the Elental® group and the control group in terms of the mean change of C-reactive protein (CRP) levels in blood serum; however, there was no significant difference in terms of a mean change of body weight and total protein level in blood serum before and after chemoradiation. Our study shows that the Elental® elemental diet could be useful for the treatment of oral mucositis induced by chemoradiation. Elental® might also promote improved completion rates of chemoradiotherapy in OSCC patients.

Introduction

Oral cancer is a subtype of head and neck cancer (HNSCC), which is within the top-10 ranking incidences of cancers worldwide (1). According to the World Health Organization, the predicted mortality rate from HNSCC could rise up to 595,000 in 2030 worldwide, which might claim approximately 324,000 lives in South East Asia alone (2). Oral cancer arises on the lip or oral cavity, and is traditionally defined as an oral squamous cell carcinoma (OSCC), because 90% of oral cancers histologically originate in the squamous cells (3,4).

The standard treatment for advanced or recurrent OSCC is surgery in combination with chemoradiotherapy (CRT) or bioradiotherapy (BRT), because these therapies can improve survival rates of patients where surgical operation only cannot provide the desired results (5). However, radiotherapy (RT) or intensified CRT can cause acute mucositis of the oral cavity, pharynx, and larynx in HNSCC patients, which poses a significant clinical problem (6,7). After the initiation of chemotherapy (CT) and/or RT, mucositis appears within 3-10 days in labial and buccal mucosa, the tongue, the floor of the mouth and soft palate (8). This often results in acute oral pain, hampered nutritional intake, and a compromised quality of life of the patients (9). Moreover, CRT-induced oral mucositis causes interruptions to RT or concurrent chemotherapy in oral cancer patients, which can prolong the hospitalization period and negatively influences patients' outcome (10-13). Current therapies against CRT-induced mucositis have shown very limited efficacy in cancer patients (14-17). Although there is no definitive treatment for preventing or curing oral mucositis, provision of adequate nutritional support, neutrophil recovery,

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Abbreviation: OSCC, oral squamous cell carcinoma

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and palliative care have shown good results for the clinical improvement of the patients (18).

Previously, we carried out a retrospective study on the efficacy of an amino-acid-rich elemental diet (ED), Elental® (EA Pharma Co., Ltd., Tokyo, Japan), for the treatment of mucositis in OSCC patients who had received CRT (5). Elental® is Japan's first ED that has been popular in Japan, as it is reported to improve the nutritional status in patients and the elderly (19). It has a well-blended mixture of several amino acids, carbohydrates, vitamins, minerals, and minimal fat and is easily digested and absorbed through the digestive tract without digestive juice secretion (19-21). It is a well-known fact that cancer can produce a state of glutamine deficiency and malnutrition in patients (22,23). Elental® is a good source of L-glutamine (2,415 mg L-glutamine/100 g Elental®) and is supposed to help in reducing the severity of CT- or RT-induced mucositis (19,20,24,25). This ED has been reported to be effective in the treatment of a number of diseases; namely, acute Crohn's disease by reducing the mucosal proinflammatory cytokine production, and stomatitis induced by chemotherapy in colorectal cancer and esophageal cancer patients (20,21,26-29). Moreover, according to one report, Elental® could counteract sarcopenia progression during CRT therapy in esophageal cancer patients and preserve lean body mass (30). Therefore, Elental® could be effective in the treatment of mucositis in OSCC patients while improving the nutritional status of the patients. Our retrospective study showed that Elental® is useful against oral mucositis in OSSC patients receiving CRT and is associated with an improved completion rate of CRT treatment in those patients (5).

This time, we carried out a prospective study to confirm the efficacy of Elental® against oral mucositis in OSCC patients and compared our new findings with those of our retrospective study. The purpose of this study was to clarify, prospectively, whether this amino-acid-rich ED is capable of minimizing or preventing RT- or CRT-induced mucositis in patients with OSCC.

Patients and methods

Patients. Fifty patients with OSCC who were scheduled for 60-70 Gy (mean 62.9 Gy) of RT with or without concurrent CRT at the Yamaguchi University Hospital of Japan from January 2015 to November 2017 participated in this study and were examined prospectively. All patients enrolled in this study were over 20 years old and had an Eastern Cooperative Oncologic Group (ECOG) performance status of 0-2. Moreover, patients who had dental caries, periodontal disease, not fitting dentures and more problems, were treated first before the administration of RT or CRT, and Elental® treatment. In some cases, tooth extraction was necessary. In that case, RT or CRT treatment and Elental® treatment was started after 2 weeks of tooth extraction. All participants gave written informed consent before entering the study. This prospective study was approved by the Institutional Review Board (IRB) of the ethics committee of the Yamaguchi University Hospital (Ref. H26-120). This study was a randomized open study (no one was blinded).

Administration of chemoradiotherapy and Elental®. All patients received conventional fractioned radiation (2 Gy per day for 5 days per week) to the oral cavity with or without concurrent chemotherapeutic agents. Concurrent chemotherapies were S-1 (65 mg/m^2/day, two-week administration and one-week rest, twice during RT), UFT (300-400 mg/day during RT), cisplatin (CDDP, 100 mg/m^2, intravenous infusion triweekly, three times during RT), Docetaxel (DOC) plus CDDP (DOC 5 mg/m^2 on day 1 plus CDDP 15 mg/m^2 on days 1-5, superselective intra-arterial infusions, 6-7 times during RT), Cetuximab (400 mg/m^2 on day 1, 250 mg/m^2 on days 8, 15, 22, 29, 36, or 43 during RT), or none (no chemotherapy, RT alone). The total treatment period of RT or CRT was for ~6-7 weeks.

The patients were assigned randomly to two groups. We prescribed Elental® (1 bottle/day) for 25 OSCC patients (Elental® group). In brief, one bottle of Elental® (80 g, 300 kcal) powder was dissolved in 300 ml water (final concentration: 1 kcal/ml), and the patients were asked to swish it around their mouths and swallow it orally once a day during the (chemo) radiation period. In addition, patients in both groups used a similar regimen of oral brushing, gargling with 4% azulene sodium sulfonate plus 4% lidocaine, and using NSAIDs and/or opioids based on each patient's pain level when they experienced severe oral pain with mucositis. We recorded data on a daily basis and compared the data from 25 patients who received Elental® (Elental® group) with those from 25 patients who did not receive Elental® (the control group) during this prospective study period. The median follow up period was 23 (8-37) months. The endpoint of the study was determined by evaluating the changes of oral mucositis in patients including the size, redness, and pain level of the affected area that received RT or CRT, and by evaluating the CRP level in patients. We finished our prospective study in March 2018.

Randomization, assessment of oral mucositis, and completion of (chemo) radiation treatments. This study was a randomized open study (no one was blinded). The degree of oral mucositis was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (National Cancer Institute CTCAE v4.0). The CTCAE v4.0 grades for oral mucositis are defined as follows: Grade 0, no mucositis; grade 1, asymptomatic or mild symptoms, and intervention not indicated; grade 2, moderate pain not interfering with oral intake, and a modified diet indicated; grade 3, severe pain interfering with oral intake; grade 4, life-threatening consequences and urgent intervention indicated; grade 5, death. Only patients without any oral disease or mucositis (grade 3 or 4) were included in the study. Briefly, all patients included in the study did not have oral mucositis (grade 3 or 4) or any other type of oral disease when we started RT/CRT and Elental® treatment. Eighteen patients were grade 0, 6 patients were grade 1, and one patient was grade 2 in Elental® group. On the other hand, 20 patients were grade 0, 4 patients were grade 1, and 1 patient was grade 2 in control group. There was no big difference between both groups.

Resident physicians and radiologists collected and documented various data of patients including the severity of mucositis, nutritional status, and efficacy of RT/CRT treatment. Oral mucositis grade was assessed by independent physicians who compared their findings with patients' personal

Table I. Clinicopathological characteristics of patients.

Characteristics	No. of patients (%)
Sex	
Male	35 (70.0)
Female	15 (30.0)
EOCG performance status	
0	25 (50.0)
1	19 (38.0)
2	6 (12.0)
Primary tumor location	
Tongue	24 (48.0)
Gingiva	22 (44.0)
Oral floor	2 (4.0)
Lip	1 (2.0)
Buccal mucosa	1 (2.0)
Stage	
I	0 (0)
II	3 (6.0)
III	14 (28.0)
IV	33 (66.0)

The mean age of patients was 68.3 years (range, 40-92 years). ECOG, Eastern Cooperative Oncologic Group.

assessment of the mouth and throat soreness, pain level, and the activity score recorded by the patients on a daily basis.

Moreover, incidence rates of grade 3 or 4 oral mucositis and completion rates of scheduled (chemo) radiation treatments by regimen were also evaluated. Treatment completion included patients who underwent all scheduled chemotherapy and >60 Gy of radiation without interruption. Furthermore, nutritional status before and after (chemo) radiation was investigated in terms of body weight and levels of total protein and C-reactive protein (CRP) in blood serum. CRP level was checked once per week during the 6-week treatment period. During the follow-up period, CRP level was examined once per week in the case of inpatients or once per month in the case of outpatients.

Statistical methods. We performed univariate and multivariate analyses to identify the clinicopathological and therapeutic factors involved in alleviation of oral mucositis during the (chemo) radiation period. P<0.05 was considered to indicate a statistically significant difference. Statistical analyses including Chi-square for independence tests, Mann-Whitney U test, unpaired Student's t-test, and multivariate logistic regression analysis were performed using StatView software (version 5.0 J, SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics. Table I summarizes the clinicopathological characteristics of all patients who participated in this study. Most of patients in this study had advanced stage OSCC (Stage III/IV), an ECOG performance status of 0 or 1, and tongue or gingival cancer. There were 35 males and 15 females with an average age of 68.3 years and range 40-92 years (Table I). Among the 50 patients, 26 developed oral mucositis grade 1 or 2, and 24 patients developed grade 3 or 4 oral mucositis after receiving RT or CRT (Table II). RT only was received by 11 patients, S-1 + RT by 8 patients, UFT + RT by 5 patients, CDDP + RT by 20 patients, DOC + CDDP + RT by 2 patients, and Cetuximab + RT by 4 patients. Half of the patients (25 patients, Elental® group) received Elental® daily (daily dose 80 g or 300 kcal/day), and half did not (control group), while receiving RT or CRT (Table II). In addition, 6 patients in the control group received a 4% azulene sodium sulfonate plus 4% lidocaine gargle, 7 patients received NSAIDs only, and 12 patients received NSAIDs plus opioids when they experienced severe oral pain with mucositis. In the case of the Elental® group, 6 patients received a 4% azulene sodium sulfonate plus 4% lidocaine gargle, 8 patients received NSAIDs only, 5 patients received NSAIDs plus opioids, and 6 patients did not receive any of the above mentioned treatments. The number of patients who needed NASIDs and/or opioids was lower in the Elental® group than in the control group.

Assessment of oral mucositis and CRT completion status after Elental® administration. We identified significant clinicopathological and therapeutic factors associated with differences in the CTCAE v4.0 oral mucositis severity grade by univariate analysis. Our data showed that Elental® administration (P=0.0002) was significantly associated with the degree of oral mucositis (Table II). The subsequent multivariate logistic regression analysis included factors with P-values of <0.05 from the univariate analysis, and the results suggested that Elental® administration (P=0.0006) was a significant factor affecting the grade of oral mucositis during RT or CRT (i.e., patients in the Elental® group mostly suffered from a lower grade of mucositis (grade 1 or 2) than the control group (Table III).

Table IV compares the characteristics of patients with Elental® administration in addition to the basic supportive care for oral mucositis (Elental® group) and patients who had only supportive care (control group). Table IV shows that the completion of treatment regimen was significantly different between the Elental® group and the control group (P=0.037). Therefore, we compared the two groups based on CTCAE v4.0 oral mucositis grade and rates of completion of RT or CRT therapy by regimen. For RT alone, 50.0% of patients in the control group had grade 3 or 4 mucositis vs. 28.6% in the Elental® group (P=0.505). For CRT, the rates of grade 3 or 4 mucositis were 77.8% vs. 4.76%, respectively, in the control group and the Elental® group (P<0.0001; Fig. 1A). Elental® showed a statistically significant difference in reducing the severity of oral mucositis in CRT cases, though the statistical significance was not observed in cases of RT alone possibly because of the small number of cases we investigated by regimen. The rates of completion by group (control vs. Elental®) were 75.0 and 100%, respectively, in RT alone (P=0.165), and 83.3 and 100% in CRT (P=0.052; Fig. 1B). Our data suggested that, although there was no statistically significant difference observed between the Elental® and control groups, Elental® still helped to reduce the interruptions of treatment regimen

Table II. Association of the grade of oral mucositis with clinicopathological and therapeutic parameters.

	Mucositis, oral by CTCAE v4.0 (n=50)		
Parameters	Grade 1 or 2	Grade 3 or 4	P-value
Sex			0.656
Male	21	14	
Female	5	10	
Age, years			0.122
≤65	15	5	
>65	16	14	
EOCG performance status			0.087
0	19	6	
1	10	9	
2	2	4	
Primary tumor location			0.834
Tongue	16	8	
Gingiva	12	10	
Oral floor	1	1	
Lip	1	0	
Buccal mucosa	1	0	
Stage			0.296
II	2	1	
III	11	3	
IV	18	15	
Total radiation dose, Gy			0.864
≤60	13	7	
>60	17	12	
Combined chemotherapy			0.075
None	7	4	
S-1	5	3	
UFT	2	3	
CDDP	17	3	
DOC + CDDP	1	1	
Cetuximab	1	3	
Elental® administration			0.0002[a]
Yes (Elental®)	22	3	
No (Control)	9	16	

[a]P<0.05 was defined as significant. CDDP, cisplatin; DOC, docetaxel; ECOG, Eastern Cooperative Oncologic Group; UFT, tegafur/uracil; S-1, tegafur/gimeracil/oteracil.

in RT and CRT cases (Fig. 1B). Here, treatment interruptions implicated the cessation of combined chemotherapy. In addition, we had to discontinue radiation treatment in four patients who belonged to the control group. The treatment interruptions happened due to oral mucositis-related severe pain and bleeding. Our data showed that Elental® was helpful in decreasing the severity of CRT-induced oral mucositis and in improving the completion rates of RT or CRT therapy regardless of the regimen.

Assessment of nutritional and inflammatory status after Elental® administration. We evaluated the nutritional and inflammatory status of patients in both groups before and after CRT and compared the changes in pre- and post-CRT nutritional or inflammatory status for each group. We retrospectively evaluated body weight, serum total protein, and CRP in blood, which is a marker for inflammation. Table V shows that there was a significant difference in CRP values between the Elental® group and the control group: A lower CRP level in serum was maintained in the Elental® group than in the control group. CRP level showed the most significant difference in the 4th to 6th week of the treatment period. However, we could not detect any significant difference in body weight or serum total protein (Table V). Also, the

Table III. Multivariate logistic regression for grade 1 or 2 oral mucositis by CTCAE version 4.0.

Variables	P-value	Odds ratio	95% CI
Elental® (vs. control)	0.0006[a]	13.037	3.037-55.961
RT + S-1 (vs. RT alone)	0.2660	0.343	0.052-2.261
RT + UFT (vs. RT alone)	0.3835	0.381	0.043-3.338
RT + CDDP (vs. RT alone)	0.1848	3.238	0.570-18.388
RT + CDDP+DOC (vs. RT alone)	0.7175	0.571	0.028-11.852
RT + Cetuximab (vs. RT alone)	0.2069	0.190	0.015-2.502

[a]P<0.05 was defined as significant. CI, confidence interval; RT, radiotherapy; CDDP, cisplatin; DOC, docetaxel; UFT, Tegafur/uracil; S-1, Tegafur/gimeracil/oteracil.

Table IV. Clinicopathological and therapeutic characteristics of Elental® treatment group vs. control group.

	No. of patients (n=50)		
Characteristics	Elental® (n=25)	Control (n=25)	P-value
Sex			0.758
Male	18	17	
Female	7	8	
Mean age, range, years	65.8 (40-92)	70.8 (40-91)	
EOCG performance status			0.215
0	14	11	
1	10	9	
2	1	5	
Primary tumor location			0.526
Tongue	13	11	
Gingiva	11	11	
Oral floor	0	2	
Lip	1	0	
Buccal mucosa	0	1	
Stage			0.723
II	1	2	
III	8	6	
IV	16	17	
Total radiation dose, Gy			0.564
≤60	11	11	
>60	14	14	
Completion of regimen			0.037[a]
Completion	25	21	
Interruption	0	4	
Combined chemotherapy			0.0573
None	4	7	
S-1	3	7	
UFT	2	3	
CDDP	14	6	
DOC + CDDP	2	0	
Cetuximab	0	4	

[a]P<0.05 was defined as significant. CDDP, cisplatin; DOC, docetaxel; UFT, tegafur/uracil; S-1, tegafur/gimeracil/oteracil.

Table V. Body weight and serum level of total protein and CRP before and after chemoradiation and their changes during the study.

	Before treatment		After treatment		Change	
Variable	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value
Body weight, kg		0.839		0.801		0.614
Elental®	49.8±12.2		48.8±12.3		-2.94±3.37	
Control	50.5±10.8		46.9±9.82		-2.80±2.58	
TP, g/dl		0.460		0.059		0.146
Elental®	6.48±0.43		5.76±0.49		-0.72±0.42	
Control	6.56±0.49		5.96±0.54		-0.57±0.51	
CRP, g/dl		0.712		0.004		0.001[a]
Elental®	0.47±0.87		1.44±1.37		0.98±0.98	
Control	0.56±0.98		4.54±4.66		3.97±3.91	

[a]P<0.05 was defined as significant. TP, total protein; CRP, C-reactive protein; SD, standard deviation.

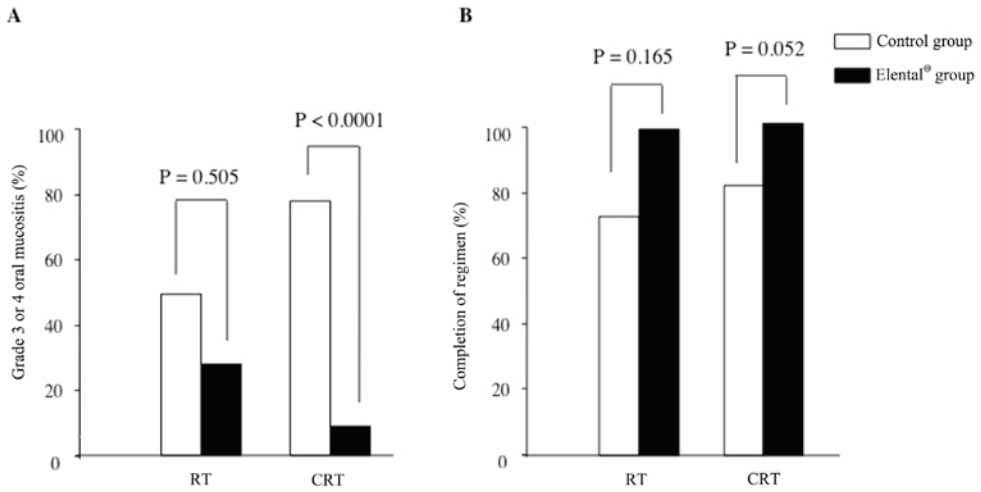

Figure 1. Effects of Elental® on oral mucositis grade and (chemo) radiation completion rate according to anticancer regimen. (A) Statistical significance was seen only in the case of grade 3 or 4 mucositis of CRT (P<0.0001); however, Elental® was associated with a tendency to decrease the severity of RT- or CRT-induced oral mucositis. (B) Elental® was associated with improved completion rates of (chemo) radiation in both RT and CRT regimens; however, a statistically significant difference was not observed between the Elental® and control groups. RT, radiotherapy; CRT, chemoradiotherapy. *P<0.05 vs. control.

number of cases that required nutrition management by tube feeding was two in the Elental® group and 10 in the control group. Two cases in the control group underwent parenteral nutrition, whereas no cases received parenteral nutrition in the Elental® group.

Discussion

In this prospective study, we demonstrated that the ED Elental® was effective for the treatment of RT or CRT-induced oral mucositis in OSCC patients. Here, BRT cases (Cetuximab + RT) were included in the CRT group because we had only 4 patients receiving BRT. Our data also showed that Elental® administration improved the completion rates of RT or CRT in OSCC patients. However, CRT completion status may not be a good indicator of Elental® efficiency because many parameters can affect CRT completion. There are some real limitations to gather enough participants by single-center study. Further multicenter study must be needed to clarify a good indicator of Elental® efficiency. We are preparing for prospective multicenter clinical trials to confirm the benefits indicated from this prospective single-center study. Basic investigations are also necessary to clarify the mechanism of action of elemental diet for (chemo) radiation-induced mucositis in OSCC.

Many HNSCC patients suffer from mucositis, swallowing disorders, and distortion of taste and smell soon after receiving CRT, followed by dysphagia, xerostomia, acute pain, trismus, osteoradionecrosis, and several dental diseases (13). Severe oral mucositis can cause unplanned breaks and delays in RT and CRT treatment, which can lead to a poor outcome for patients (31,32). These CRT side effects can also negatively affect the patient's ability to eat and drink, which can result in malnutrition, dehydration, and weight loss (33,34). Therefore, patients might require additional nutritional supplements. There are many nutritional supplements with L-glutamine that are prescribed for cancer patients, because L-glutamine

can encourage protein synthesis and enterocyte proliferation and is reported to be useful in reducing inflammation (35,36). Moreover, *in vivo* animal studies have demonstrated the safety of glutamine supplements and its ameliorating effect against cytotoxicity-induced mucositis (24,25,37).

Elental®, with a high L-glutamine content, has been used in Japan for four decades, and its safety has been well established (5,19,20). It costs <US$4.00 per day and has been approved and covered by public insurance as a prescription medication for the treatment of malnutrition in Japan (19). It has almost the same formula as VIVONEX® T.E.N. (Nestlé, Vevey, Switzerland) prescribed in many Western countries (38). Elental® has been reported to be effective against various gastrointestinal disorders, such as inflammatory bowel disease or Crohn's disease (26,27,39,40). Several authors have reported the benefits of Elental® against oral mucositis during CT and/or RT in patients with esophageal, colorectal, and oral cancer while preserving the lean body mass of patients (5,28-30). Compared to other treatment options available for mucositis in cancer patients, Elental® could be an attractive agent because it is neither costly nor a growth factor such as palifermin, and no side effects of Elental® have been reported thus far (5,14,29,39,41). However, only a few published reports are available on the efficacy of Elental® for the treatment of RT and/or CT-induced oral mucositis (5,37).

The preventive and healing effects of Elental® against oral mucositis have been assessed in several clinical trials, but very few were carried out prospectively or with randomization (23,28,42). Previously, we carried out a retrospective study that showed the effectiveness of Elental® against oral mucositis in OSSC patients receiving CRT (5). Our present study was conducted prospectively on OSCC patients with CRT-induced mucositis. We observed similar data as our previous retrospective study, which confirms the ameliorating effect of Elental® against oral mucositis. In this study, we observed a significant association (P=0.0002) between Elental® administration and the degree of oral mucositis by univariate analysis. Our multivariate logistic regression analysis also showed that patients in the Elental® group mostly suffered from a lower grade of mucositis (grade 1 or 2) than the control group (P=0.0002). Moreover, OSCC patients who received Elental® showed an improved completion rate of RT or CRT compared to the control group. We did not detect any adverse effects in relation to the clinical use of Elental® in this study (data not shown).

We assessed the CRP level in the blood of patients because a high level of CRP is considered as a marker of inflammation. Our data showed that administration of Elental® was associated with suppressed expression of CRP. However, because CRP is increased by various factors, its relation to mucositis grade is still unclear. According to our *in vitro* data, Elental® treatment could successfully downregulate the expression of inflammatory cytokines in the immortalized human keratinocyte cell line HaCaT (43). Therefore, we assumed that Elental® might suppress CRP expression via the downregulation of inflammatory cytokines. We also showed previously that Elental® can treat mucositis and dermatitis by accelerating mucosal and skin recovery through FGF2 induction and reepithelization *in vivo* (37). CRT- or RT-induced mucositis occurs through a sequence of stepwise events, namely, direct DNA damage leading to cell damage, followed by the activation of several transcription factors including nuclear factor-κB (NF-κB), Wnt, and p53, and their molecular pathways (43). Therefore, it is important to understand whether these factors and molecular pathways are affected by Elental® treatment or not. There could be other factors that contribute to the development and degree of oral mucosistis, and consumption of Elental® alone might not be able to reduce the severity of oral mucositis induced by more RT or CRT regimens that are more intensive than those administered in our current study. In order to clarify the mechanism underlying the efficacy of Elental® against oral mucositis in OSCC, further investigations are necessary.

Our study did not show some of the desired results expected by nutritional supplementation. According to several reports, Elental® nutrition therapy has supportive effects in patients with Crohn's disease and esophageal cancer, including nutritional status improvement and average body mass index preservation (26,27,30). However, we did not find any association between Elental® administration and the improvement of nutritional status (total protein) or body weight of OSCC patients in this study. Therefore, the effect of Elental® on the maintenance of nutritional status of patients should be clarified by future, randomized clinical trials. Moreover, only 2 patients in the Elental® group required tube feeding as a nutrition therapy, whereas it was 10 patients in the control group. In addition, the control group received only central venous alimentation. Additional clinical data are needed to clarify the reason behind the marked decreases of oral intake that were seen in the control group patients.

Our present prospective clinical trial demonstrated that Elental® is beneficial in the treatment of oral mucositis for OSCC patients receiving CRT or BRT and can also improve the chemo (radiation) treatment completion rate. Thus, it confirmed the findings of our previous retrospective study on the usefulness of Elental® against oral mucositis in OSSC patients. These findings warrant the initiation of future prospective studies with a larger group of patients to confirm further the efficacy of Elental® for RT- or CRT-induced oral mucositis.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

KH assisted in the study design, performed the study and data analysis, and wrote the manuscript. HaM carried out the prospective study and collected data from patients. TF carried out data evaluation and assisted in manuscript

writing. HaM, YK, HU, DH, KU, SP, SC, HH, ST, MO, HiM, JM, HK, SA, and KS helped to carry out the prospective study and helped in data collection. KM helped with data collection and analysis, and edited and revised the manuscript. All the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This prospective study was approved by the Institutional Review Board (IRB) of the Ethics Committee of the Yamaguchi University Hospital (Ref. H26-120). All procedures performed in the studies involving human participants were in accordance with the standards of the ethics committee of the Yamaguchi University Hospital. Written informed consent was obtained from all individual who participated in this study. Clinical trial registration no. H26-120, name of registry: Efficacy of enteral nutrition on chemoradiotherapy against oral cancer, date of registration: January 23, 2015.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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