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A prospective pilot study of an elemental nutritional supplement for prevention of oral mucositis during S-1 adjuvant chemotherapy for gastric cancer

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ABSTRACT

Purposes: Oral mucositis is one of the most common reasons for discontinuation of S-1 adjuvant chemotherapy after radical gastrectomy. Some studies suggest that nutritional support with amino acids may improve oral mucositis. We conducted a prospective, randomized clinical trial of patients who underwent adjuvant chemotherapy for gastric cancer to examine whether an oral elemental diet prevents chemotherapy associated oral mucositis and body weight loss.

Methods: Patients were randomly assigned to a group consuming Elental® (the treatment group, n = 11) or a control diet group (n = 11). Patients in the treatment group consumed one pack of Elental® per day during adjuvant chemotherapy. The primary endpoint was the presence and grade of oral mucositis. Secondary endpoints included adherence to Elental® based on the doses recorded in a diary, changes in nutrition parameters, and frequency and severity of adverse events.

Results: The incidence of oral mucositis was significantly lower in the treatment group (9.1%) than in the control group (27.3%). The median body weight loss in the treatment group was significantly smaller than that in the control group (P = .015). According to Kaplan-Meier estimates the treatment group was significantly associated with high cumulative S-1 continuation rates (log-rank P = .047).

Conclusion: We conclude that the amino-acid-rich elemental diet Elental® may be useful as a countermeasure for S-1 adjuvant chemotherapy-induced mucositis.

1. Introduction

Gastric cancer is the fifth most common cancer worldwide and is the third leading cause of cancer-related death, with an especially high incidence in East Asian countries such as Japan, China, and Korea [1]. In East Asia, gastrectomy with D2 dissection has long been a standard radical treatment for localized gastric cancer. Recently, adjuvant chemotherapy has been added following surgery for pathological stage II and III gastric cancer because 2 randomized trials have demonstrated a significant survival benefit [2,3]. The ACTS-GC trial demonstrated that S-1 was effective as adjuvant chemotherapy for Japanese patients who underwent curative gastrectomy for locally advanced gastric cancer and were diagnosed as having pathological stage II or III cancer [3]. Therefore, adjuvant S-1 chemotherapy has been established as the standard therapy for stage II and III gastric cancer in Japan. The aim of adjuvant chemotherapy is to eradicate micrometastatic tumor cells; to do so, it is essential to continue chemotherapy for a minimal length of time. However, continuation of S-1 is sometimes difficult for patients who are unable to maintain satisfactory oral feeding. For example, the ACTS-GC trial showed that the continuation rate of S-1 administration was 65.8% at 12 months after surgery [3].

Although the relationship between the S-1 continuation rate and prognosis remains unclear, lower compliance with S-1 might lead to an unfavorable prognosis. The most common cause of withdrawal was the occurrence of adverse events. It is important to identify risk factors for the continuation of S-1 adjuvant chemotherapy, because physicians can then support patients accordingly. Several retrospective studies pointed out that body weight loss after surgery, older age, and complications

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after surgery are independent risk factors [4,5]. However, there are few prospective studies that have investigated the continuation of S-1 adjuvant chemotherapy.

Oral mucositis is an acute ulcerative inflammation of the oral mucosa associated with direct drug toxicity and myelosuppression. Approximately 50% of patients undergoing S-1 adjuvant chemotherapy for gastric cancer develop the condition [6]. Oral mucositis is a distressing condition because of severe pain and bleeding, which may compromise oral hygiene and nutrition and increase the risk of local or systemic infection. Thus, oral mucositis can lead to reduction of chemotherapy dosage or outright discontinuation. However, no methods of prevention have yet been well established. Recently, some reports showed that the elemental diet preparation Elental® may prevent oral mucositis in patients undergoing chemotherapy for esophageal and colorectal cancer [7,8].

We conducted a prospective, randomized clinical trial of patients who underwent adjuvant chemotherapy for gastric cancer to see how nutritional support with amino acids influenced adverse effects associated with chemotherapy. We used Elental® (Ajinomoto Pharmaceutical Co. Ltd, Tokyo, Japan) because this agent is one of the most popular nutrition products and contains a well-balanced blend of amino acids and minerals.

This article is a preliminary report evaluating the effectiveness of oral nutritional support with amino acids for prevention of chemotherapy-induced oral mucositis or diarrhea.

2. Patients and methods

2.1. Patients

Patients were eligible for this study if they met the following inclusion criteria: histologically proven gastric cancer, clinical stage II or III disease, age from 20 to 80 years, an Eastern Cooperative Oncology Group performance status of 0–2, curative resection, no prior chemotherapy or radiation therapy, and no history of gastrectomy or other malignancy (except uterine cervical carcinoma in situ and focal colorectal adenocarcinoma) during the past 5 years. Exclusion criteria included severe heart disease, interstitial pneumonia or pulmonary fibrosis, bleeding tendency, liver cirrhosis or active hepatitis, chronic renal failure, severe diabetes (HbA1c > 9.0%), and severe drug allergy. All patients gave written informed consent before undergoing randomization.

All patients had undergone curative distal or total gastrectomy for gastric adenocarcinoma at Gunma University Hospital from November 2011and to September 2014. Patients were invited to participate in the study after they underwent surgery.

The authors recruited 40 patients according to the described criteria, and 22 of these patients participated in the present study (Fig. 1). This study was approved by the Institutional Review Board of the Gunma University Graduate School of Medicine and was in accordance with the ethical guidelines of the Declaration of Helsinki.

2.2. Administration of chemotherapy and Elental®

The patients received 80 mg/m2 of S-1 on days 1–28 of every 42-day cycle. During the study period, patients in both groups consumed a regular diet without any restriction. In addition, patients in the treatment group consumed one pack of Elental® (Table 1) per day on day 1–28 for 2 courses of chemotherapy. The supplements were consumed as a solution of one pack with 250 mL water (total volume = 300 mL liquid) or with 150 mL water plus agar powder (total volume = 200 mL jelly). Patients could select either form of Elental® at any time of the day, regardless of meal times. Patients in the control group continued their regular diet alone during the study.

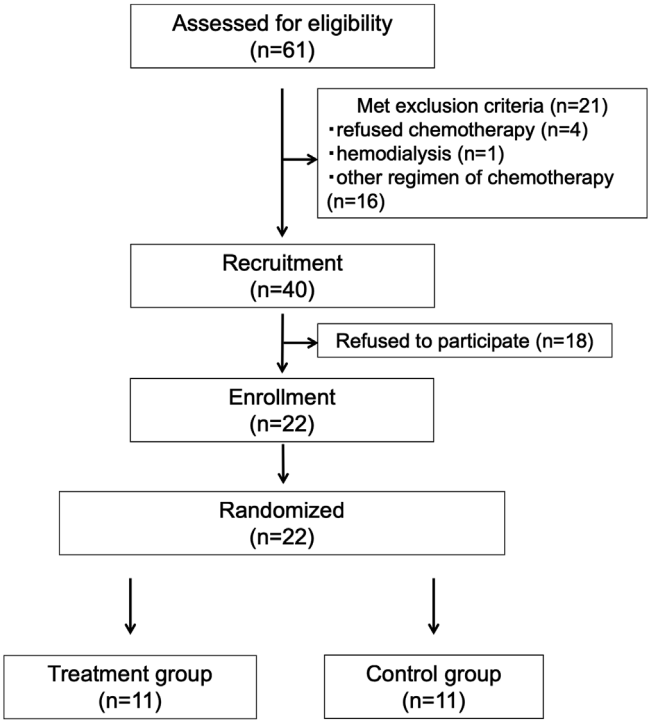

Fig. 1. CONSORT diagram.

Table 1
Composition of Elental® (one package = 80 g).

Energy		300 kcal	
Carbohydrate (Dextrin)	63.41 g	Vitamin A	648 IU
Fat (Soybean oil)	0.51g	Vitamin D	1.3 μg
Amino acid	14.1g	Vitamin B-1	194 μg
		Riboflavin sodium phosphate	256 μg
L-Isoleucine	642 mg	Vitamin B-6	267 μg
L-Leucine	899 mg	Niacin	2.20 mg
Lysine hydrochloride	888 mg	Pantothenic acid Ca	1.19 mg
L-Methionine	648 mg	Folic acid	44 μg
L-Phenylalanine	871 mg	Vitamin B-12	0.7 μg
L-Threonine	523 mg	Vitamin C	7.80 mg
L-Tryptophan	151 mg	Vitamin K	9 μg
L-Valine	701 mg	Vitamin E	3.30 mg
L-Histidine hydrochloride monohydrate	501 mg	Biotin	39 μg
L-Arginine hydrochloride	1125 mg	Choline bitartrate	17.93 mg
L-Alanine	899 mg	Citric acid hydrate	616 mg
L-Aspartic acid magnesium potassium	1036 mg	Calcium glycerophosphate	825 mg
L-Aspartic acid sodium monohydrate	867 mg	Ferrous gluconate	15.5 mg
L-Glutamine	1932 mg	KCl	150 mg
Aminoacetic acid	505 mg	$ZnSO_4$	7.88 mg
L-Proline	630 mg	$MnSO_4$	1.30 mg
L-Serine	1159 mg	$CuSO_4$	0.82 mg
L-Tyrosine	110 mg	KI	19.6 μg

2.3. Study design

This study was a randomized open-label study. The patients were randomly assigned to the treatment group or the control diet group. A coordinating center (Gunma University Hospital Clinical Trial Center) generated the treatment allocation codes using a computer-generated randomization table.

2.4. Endpoints and assessments of oral mucositis and diarrhea

The primary endpoint was the presence and grade of oral mucositis. Patients completed daily questionnaires during the study period. The grades of oral mucositis and of diarrhea were determined in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Finally, oral mucositis was assessed by independent physicians, who were blinded whether administered or not, based on the patient's self-assessment and the maximum grade of oral mucositis at each chemotherapy course was recorded. Secondary endpoints included adherence to Elental® based on the doses recorded in a diary, changes in nutrition indicators (serum total protein, serum albumin, retinol binding protein, transthyretin, and transferrin), and frequency and severity of adverse events. Blood samples for evaluation of efficacy and safety were regularly collected during the study and were analyzed by a biochemical laboratory.

2.5. Statistical analysis

We planned to enroll a sample size of 60 patients with a power of 80% for the two-sample *t* test at a two-sided significance level of 0.05 to detect superiority of the elemental diet to the control group in terms of the percentage of stomatitis. Statistical analyses were performed using Student's *t* test or Fisher's exact test. A P value $< .05$ (two-sided) was considered statistically significant. Statistical analyses were performed with JMP version 13.0.0 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

A total of 22 patients were enrolled. The background characteristics of patients are shown in Table 2. Patient ages ranged from 59 to 80 years. Total gastrectomy was performed in 8 patients, and a laparoscopic approach was used in 4 cases. The median body weight loss in the treatment group was significantly smaller than that in the control group ($P = .015$).

3.2. Treatment compliance rate of Elental®

In the treatment group, the degree of compliance with Elental® was determined based on the patients' self-reported diaries as the percentage of the prescribed dose of Elental® consumed each day. The mean treatment compliance rate in the Elental group was 71.4% ± 22.4%, with a median value of 81.3%.

3.3. Oral mucositis

The incidence of oral mucositis was significantly lower in the treatment group (9.1%) than in the control group (27.3%) (Fig. 2).

3.4. Continuation rate of S-1 and risk factors

Fig. 3 shows the Kaplan-Meier estimates of cumulative S-1 continuation rates according to the treatment and control groups. The treatment group was significantly associated with higher cumulative continuation rates (log-rank $P = .047$). Each clinicopathological factor was categorized as shown in Table 3, and was analyzed for risk of S-1 continuation. Univariate analyses demonstrated that stomatitis was the only significant risk factor.

3.5. Adverse events

All patients in the treatment and control groups were included in the safety analyses (Table 4). There were six Grade 2 adverse events. The incidences of hematological and non-hematological adverse events were not significantly different between the groups.

Table 2
Characteristics of the patients at baseline (before chemotherapy).

	Control (n = 11)	Elental (n = 11)	P Value
Age (years)	67.1 (59–80)	68.4 (61–80)	0.302
Gender			0.611
Male	8	9	
Female	3	2	
Performance status (ECOG)			0.338
0	7	9	
1	4	2	
Type of gastrectomy			0.375
Distal	6	8	
Total	5	3	
Operation methods			0.269
Open	10	8	
Laparoscopic	1	3	
Tumor size(mm)	54.91	54.55	0.487
Depth of invasion			0.611
mp	2	3	
> ss	9	8	
Lymph node metastasis			0.138
Negative	2	0	
Positive	9	11	
Stage of disease			0.190
II	6	3	
III	5	8	
Complications			0.534
Present	2	1	
Absent	9	10	
Body weight loss	15.75	12.59	0.015
White blood cell count	6500 ± 458.3	5475 ± 892.1	0.133
Neutrocyte count(%)	64.67 ± 11.24	62.75 ± 8.92	0.810
Platelet count	232.0 ± 65.83	217.8 ± 80.39	0.813
Hemoglobin	10.87 ± 1.78	11.93 ± 1.24	0.392
AST	55.0 ± 18.24	55.25 ± 27.08	0.989
ALT	50.33 ± 4.16	54.75 ± 11.44	0.559
Total bilirubin	0.93 ± 0.25	0.88 ± 0.22	0.758
Creatinine	0.80 ± 0.47	1.08 ± 0.28	0.363
Total protein	5.80 ± 0.46	5.50 ± 0.54	0.472
Albumin	3.77 ± 0.32	3.88 ± 0.43	0.729
Retinol binding protein	3.13 ± 1.07	2.85 ± 0.74	0.693
TTR	24.90 ± 8.49	24.53 ± 5.15	0.944
Transferin	231.0 ± 74.0	208.8 ± 91.09	0.744

4. Discussion

To our knowledge, this is the first study to show that the elemental diet Elental® is associated with lower incidence and severity of oral mucositis in patients with advanced gastric cancer receiving S-1 adjuvant chemotherapy.

The mechanism of chemotherapy-induced oral mucositis remains unclear. However, it has been reported that oral glutamine might prevent chemotherapy-associated mucositis [9,10]. Moreover, Peterson et al. reported that Saforis™, a sustained-release preparation of glutamine, was associated with significantly lower rates of oral mucositis in cancer patients receiving chemotherapy [11]. Glutamine could be important in preventing oral mucositis induced by chemotherapy. However, in general, the systemic administration of L-glutamine alone was not recommended by the Clinical Practice Guidelines for Prevention and Treatment of Mucositis of the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology in 2007 [12]. In the present pilot study, we examined whether the elemental diet Elental® (one pack 80 g/300 kcal), which contains 1932 mg of L-glutamine, can prevent oral mucositis in patients with advanced gastric cancer during S-1 adjuvant chemotherapy. According to 2 reports, Elental® was associated with reduced incidence and severity of oral mucositis in patients receiving chemotherapy for esophageal cancer and colorectal cancer respectively [7,8]. Our data are in line with these reports.

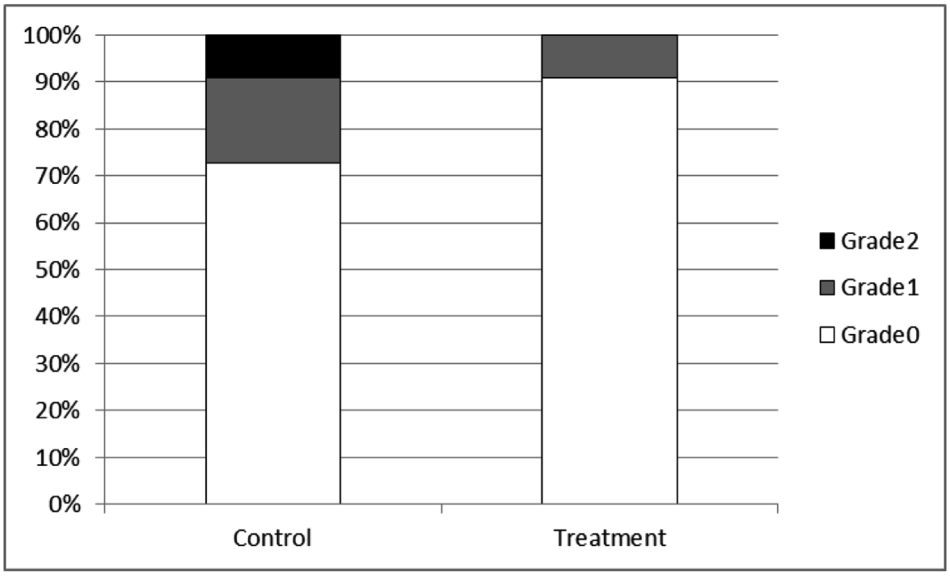

Fig. 2. Incidence of oral mucositis during study (%).

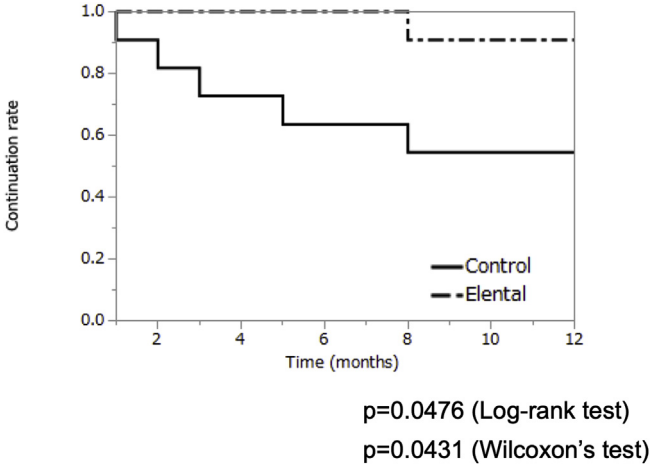

Fig. 3. Comparison of the S-1 adjuvant chemotherapy continuation rate in the control group and elemental diet treatment group.

After undergoing gastrectomy, patients may be unable to digest food due to depressed gastric reservoir function and gastrointestinal functional changes such as insufficient digestion and absorption. Moreover, patients who receive adjuvant chemotherapy are more likely to lose weight due to malnutrition and anorexia caused by chemotherapy-associated gastrointestinal toxicities. Imamura et al. showed that the Elental® treatment group lost significantly less weight compared with the control group after gastrectomy [13]. This study strongly supports our result. We cannot explain the mechanism for the maintenance of body weight, because we did not have enough data. However, it was recently reported that enteral administration of amino acid mixtures was associated with normal amino acid absorption in patients with mucositis [14]. We think that amino acids may be more suitable than proteins for patients with depressed gastric reservoir function and gastrointestinal functional changes.

The present study showed that the continuation of S-1 adjuvant chemotherapy in the Elental® treatment group was significantly higher than in the control group and that oral mucositis was a significant risk factor for continuation of S-1 adjuvant chemotherapy. There are several limitations in our study. First, it was a single-institutional study with a small sample size. Second, we did not exclude patients who experienced recurrence within 12 months after surgery. However, we think that Elental® treatment can affect the continuation of S-1 adjuvant chemotherapy, for several reasons.

Severity of neutropenia has been associated with the incidence and severity of chemotherapy-induced oral mucositis [15]. Ogata et al. demonstrated that the severity of oral mucositis tended to increase with the severity of neutropenia [7]. This study encourages us to speculate on whether nutritional intervention could also improve neutropenia.

Body weight loss was the second strongest risk factor for continuation of S-1 adjuvant chemotherapy even though it was not significant in the present study. Aoyama et al. showed that body weight loss of 15% or higher was associated with significantly lower S-1 compliance in patients with gastric cancer, and reasons for withdrawal were anorexia and fatigue [4]. Ryu et al. found that postoperative body weight loss was significantly greater in malnourished patients than in well-nourished patients [16]. Therefore, body weight loss was found to closely correlate with a decline in postoperative quality of life and could be one indicator of malnutrition. A decrease in physiological function might affect compliance with S-1 chemotherapy, although the precise mechanisms are still unknown. One of the limitations of our study was the small sample size studied at a single site. Hence, we are currently conducting a large, multicenter study to confirm the beneficial effects of Elental® on adjuvant chemotherapy induced oral mucositis in gastric cancer patients.

We conclude that the amino-acid rich elemental diet Elental may be useful as a countermeasure for S-1 adjuvant chemotherapy-associated mucositis. It could affect continuation of S-1 adjuvant chemotherapy in patients with advanced gastric cancer. Further prospective multicenter clinical trial must be needed to confirm the benefits indicated from this prospective single-center study.

Disclosures

No conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://

Table 3
Univariate and multivariate Cox proportional hazards analyses of clinical factors for S-1 continuation.

Clinical factors	No.	Univariate			Multivariate		
		HR	95%CI	P value	HR	95%CI	P value
Age (years)				0.264			
< 70	12	1.000					
≥70	10	2.542	0.496–18.33				
Gender				0.524			
Male	17	1.000					
Female	5	1.773	0.246–9.092				
Performance status (ECOG)				0.161			
0	16	1.000					
1	6	3.249	0.600–17.59				
Type of gastrectomy				0.415			
Distal	14	1.000					
Total	8	1.958	0.362–10.59				
Body weight loss				0.081			
< 15	14	1.000					
≥15	8	4.290	0.834–31.04				
Stomatitis				0.018			0.018
No	18	1.000			1.000		
Yes	4	8.459	1.498–47.98		8.459	1.498–47.98	
Stage of disease				0.683			
II	9	1.000					
III	13	1.416	0.276–10.22				

Table 4
Incidence of grade 2 adverse events.

	Control (n = 11)		Elental (n = 11)	
	Grade 1	Grade 2	Grade 1	Grade 2
Diarrhea	1			1
Anorexia	2		1	
Nausea	1			
Anemia		1		1
Neutropenia		1	1	
Elevated AST			1	
Elevated ALT	1	1		1
General fatigue	1		1	

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