Original Article

A prospective study of nutritional supplementation for preventing oral mucositis in cancer patients receiving chemotherapy

Takuya Okada MD, Yasuaki Nakajima MD, Tetsuro Nishikage MD, Tairo Ryotokuji MD, Yutaka Miyawaki MD, Akihiro Hoshino MD, Yutaka Tokairin MD, Kenro Kawada MD, Kagami Nagai MD, Tatsuyuki Kawano MD

Department of Esophageal Surgery, Tokyo Medical and Dental University, Japan

Background and Objectives: Patients undergoing chemotherapy often develop distressing adverse effects such as oral mucositis and diarrhea. Nutritional support with elemental diet is effective against various gastrointestinal complications and may exert protective effects against adverse effects induced by chemotherapy. To evaluate the influence of elemental diet on chemotherapy-induced oral mucositis and diarrhea, we conducted a randomized control trial in patients with esophageal cancer undergoing chemotherapy. **Methods and Study Design:** Twenty esophageal cancer patients receiving chemotherapy with 5-fluorouracil plus cisplatin were assigned randomly to one of the following two groups: (1) receiving elemental diet with Elental (one pack per day) for 14 days and (2) not receiving Elental during chemotherapy. The severity of oral mucositis and diarrhea was graded using clinical examination by doctors and a standard questionnaireon days 1-14. **Results:** Based on the analysis of the standard questionnaire, the distribution of the maximum severity of oral mucositis showed a statistically significant reduction in the Elental group (p=0.020), while clinical examination showed insignificant reduction but shift toward lower grade. In the Elental group, the incidence of oral mucositis (grade ≥2) reduced consistently and the median grade was lower at all-time points. Regarding diarrhea, no difference was observed between the two groups based on the analysis of the standard questionnaire and clinical examination results. **Conclusions:** This study illustrates the effectiveness of oral elemental diet in preventing oral mucositis during chemotherapy. This is a preliminary report and further study with larger patients groups should be devoted to optimization of efficacy.

Key Words: chemotherapy, oral mucositis, diarrhea, elemental diet, sophageal cancer

INTRODUCTION

Chemotherapy is an inevitable modality of current cancer treatment, and its efficacy has been an important factor influencing the prognosis of cancer patients. Anticancer drugs often induce severe adverse effects that may preclude the patients from completing chemotherapy. The most serious complications by chemotherapy include myelosuppression, hepatic or renal disorder, and oral mucositis or diarrhea. Oral mucositis is an acute ulcerative inflammation of the oral mucosa caused by direct drug toxicity and myelosuppression.[1] Approximately 40% of patients undergoing chemotherapy develop oral mucositis, with the higher rate being >90% in children.[2] Oral mucositis is a distressing condition because of severe pain, bleeding or dysgeusia, which may compromise oral hygiene and nutrition, and increase the risk of local or systemic infection.[3] Thus, oral mucositis can cause a discontinuance of chemotherapy or reduction of dosage.[4] However, the methods of prevention have not been established well.

As esophageal squamous cell carcinoma (ESCC) is one of the most sensitive cancers to chemotherapy and radiation, the treatments for ESCC are commonly planned in combination with several modalities; e.g. chemotherapy with/or radiation, before or after surgery. These treatments themselves or the adverse effects from them easily influence the nutrition status of the patients, and the rate of malnutrition in patients with esophageal cancer is reported to be the hihest among all cancers, 60-85%.[5] Good control of the side effects or the nutrition status is inevitable for making the treatments more successful and more effective.[6,7]

We are conducting a prospective, randomized clinical trial to ESCC patients, to see how the nutritional support with amino acids influenced the adverse effects from chemotherapy. As a supplement of amino acids, we use 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

Corresponding Author: Dr Yasuaki Nakajima, Department of Esophageal Surgery, Tokyo Medical and Dental University, Yushima 1-5-45, Bunkyo-ku, Tokyo 113-8519, Japan.
Tel: +81-3-5803-5254; Fax: +81-3-3817-4126
Email: yasu.nakajima.srg1@tmd.ac.jp
Manuscript received 02 August 2015. Initial review completed 31 August 2015. Revision accepted 21 September 2015.
doi: 10.6133/apjcn.112015.03

amino acids and minerals. Elental has been proven to be effective against various gastrointestinal disorders, such as inflammatory bowel disease (IBD).[8,9]

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

METHODS

Patients

A randomized clinical trial was conducted at Tokyo Medical and Dental University Hospital. This study included patients who were diagnosed with squamous cell carcinoma of esophagus histopathologically, and referred for chemotherapy protocol with 5-fluorouracil (5-FU) plus cisplatin. Patients with both chemotherapy and radiation simultaneously were excluded for eliminating the direct effects by radiation damage. All patients in this study were 18 years of age or older, and no patient had a history of oral complications or immunodeficiency before chemotherapy. The patients were requested not to smoke or chew tobacco for at least 2 months before chemotherapy. As a routine prophylaxis of oral mucositis, all patients were medicated with a gargle containing 0.08% lidocaine. Whether the patients had previously undergone surgery was not a condition for inclusion in the study. By using the enveloped method, the enrolled patients were randomized into two groups: (1) receiving elemental diet for the duration of chemotherapy and (2) not receiving elemental diet for the duration of chemotherapy (Control Group). Twenty-two patients were enrolled, with 11 patients in each group. One patient from each group dropped out from this study at their own request, but they continued with their chemotherapy program. Thus, 10 patients in each group completed chemotherapy and were included in analysis (Figure 1).

All patients provided written informed consent. The study protocol and the informed consent disclosure were in accordance with the precepts established by the Helsinki Declaration and approved by the Clinical Research Center of Tokyo Medical and Dental University Hospitalas number 22-19. This study has been also registered in the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as number UMIN 000004898.

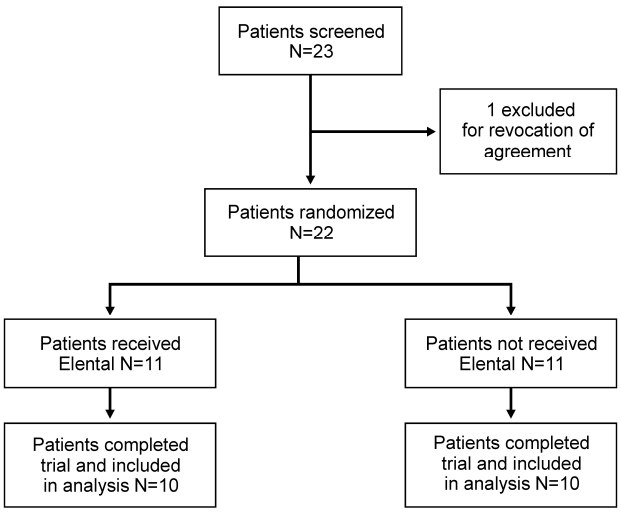


Figure 1. Patient screening, enrolment, and follow-up

Chemotherapy regimen

Cisplatin was administered at a dose of 80 mg/m^2 by slow drip infusion on day 1, and 5-FU was administered at a dose of 800 mg/m^2 per day by continuous infusion for 24 h on days 1-5.

Elemental diet

The elemental diet used for the patients in the intervention group was Elental. These patients ingested one pack of Elental per day on days 1-14. 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. Each treatment was conducted under the supervision of medical staff in order to record the daily intake and the onset of oral mucositis or diarrhea.

Laboratory tests

The control and Elental groups were compared with respect to the baseline values of body mass index (BMI), white blood cell (WBC) count, lymphocyte and neutrophil counts, Total protein, albumin, hemoglobin (Hb), platelet (Plt), total cholesterol (T-chol), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), blood urea nitrogen (BUN), and creatinine (Cre). BMI was calculated as the patient's body weight divided by the square of the height. These measured values and laboratory data were obtained the day before the initiation of chemotherapy.

Assessment of oral mucositis and diarrhea

Doctors who specialize in chemotherapy evaluated oral mucositis and diarrhea of each patient, with clinical examinationas objective data. Moreover, daily questionnaire was recorded on days 1-14 as subjective change of symptoms. The grades of oral mucositis and diarrhea were determined in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical analysis

The baseline characteristics of patients were compared using the unpaired *t*-test, the maximum severity of oral mucositis and diarrhea with the Wilcoxon rank sum test, and the correlation between Elental intake and maximum severity of oral mucositis with the Spearman rank correlation test. All tests were two-tailed, with the level of significance set at $p<0.05$. All analyses were performed using SAS software, v9.2.

RESULTS

Characteristics of patients

The baseline characteristics of patients are summarized in Table 1. No statistically significant differences were observed in the gender, age, BMI, WBC, Lymphocyte, Neutrophil, Total protein, Albumin, T-chol, Hb, Plt, AST, ALT, T-Bil, BUN, Cre of the Elental group and Control group.

Safety and tolerance of Elental

Of the 10 patients in the Elental group, two completed the entire pack each day for 14 days. Another two patients adjusted their intake to a comfortable dose and completed the treatment of 14 days, and four patients took a fraction of the pack each day. The rest of two patients suspended the Elental ingestion by themselves on day 8. The average Elental intake rate of the Elental group during the treatment period was 61% (17.9%-100%), and seven patients consumed more than 50% of the total Elental treatment. Nosevere complications associated with Elental occurred.

Efficacy of Elental

The distribution of maximum severity of oral mucositis based on the responses to the standard questionnaire showed a statistically significant shift toward lower grade in the Elental group during 5FU/cisplatin chemotherapy (p=0.020). The maximum grade of oral mucositis evaluated with clinical examination also declined in the Elental group compared with the control group, but without statistical significance (Table 2). The incidence of CTCAE grade ≥2 by clinical examination on each day was recorded, and the proportion of patients with CTCAE grade ≥2 was lower consistently in the Elental group than control group (Figure 2).

With regard to the occurrence of diarrhea during chemotherapy, no difference between two groups was observed based on the analysis of the standard questionnaire and clinical examination results (Table 3).

DISCUSSION

Many studies regarding the prevention of oral mucositis induced by chemotherapy have been reported previously, and some of the preventive methods are actually adapted to the cancer patients in clinical use; e.g. mouthwashes, analgesia or cryotherapy with ice.[10-12] Elental, the same elemental diet as this study, has been also used in several clinical trials for evaluating its preventive effect.[13,14] However, most of the previous studies were carried out retrospectivelyor without randomization, and our ongoing study has a significant meaning as the first prospective, randomized control trial for evaluating the preventive effect by additional nutrition support.

Recently, a major topic for effective cancer treatment is

Table 1. Baseline characteristics of patients

	Elental group	Control group	Normal value	p value
Gender, M/F	9/1	8/2	-	0.527
Age	65.3	67.1	-	0.660
BMI	21.4	22.1	18.5-24.9	0.677
White blood cells (/μL)	6,980	6,590	3,500-9,800	0.738
Lymphocyte (/μL)	1,542	1,694	1,500-4,000	0.569
Neutrophil (/μL)	5,187	4,380	1,830-7,250	0.449
Total protein (g/dL)	6.99	7.26	6.5-8.0	0.263
Albumin (g/dL)	4.65	4.30	3.7-5.2	0.640
Total cholesterol (mg/dL)	168	200	120-220	0.360
Hemoglobin (g/dL)	12.4	13.1	M: 14-18; F:11-15	0.230
Platelets ($\times 10^4$/μL)	26.9	26.4	15-40	0.920
AST (U/L)	21.1	19.6	10-35	0.640
ALT (U/L)	17.3	15.2	5-40	0.680
Total bilirubin (mg/dL)	0.48	0.57	0.2-1.0	0.260
BUN (md/dL)	13.5	14.1	8-20	0.720
Serum creatinine (mg/dL)	0.71	0.80	M: 0.7-1.2; F:0.5-0.9	0.120

BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen.

Table 2. Distribution of maximum severity of oral mucositis in FP treatment cycle

Group		Oral mucositis grade				p value*	% grade ≥2
		0	1	2	3		
By standard questionnaire	Elental group	0	6	3	1	0.020	40
	Control group	0	1	4	4		80
By clinical examination	Elental group	4	4	2	0	0.078	20
	Control group	2	0	5	2		70

*Wilcoxon rank sum test.

Table 3. Distribution of maximum severity of oral mucositis in FP treatment cycle

Group		Diarrhea grade			
		0	1	2	3
By standard questionnaire	Elental group	4	4	1	1
	Control group	5	4	1	0
By clinical examination	Elental group	6	3	1	0
	Control group	6	3	1	0

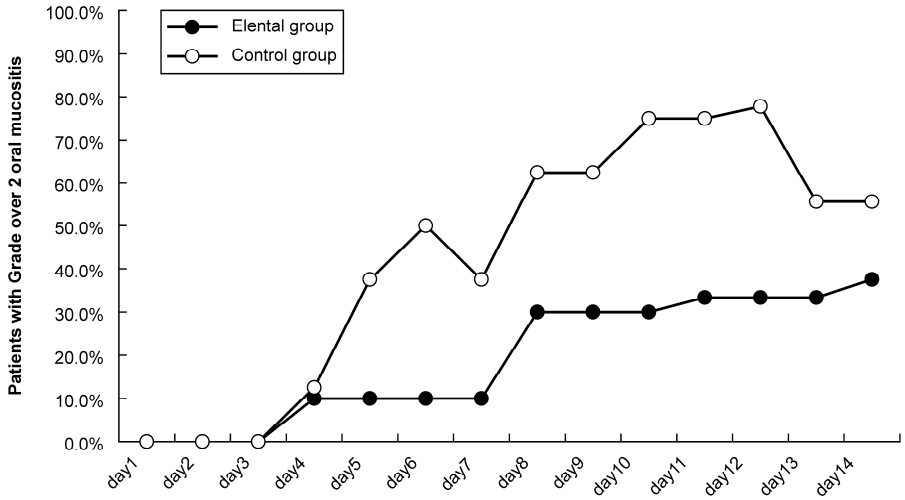


Figure 2. Percentage of patients with CTCAE grade over 2 oral mucositis at each time point during chemotherapy

the evaluation and the management of nutritional status of the patients.[15] Nutritional disorders often occurs in cancer patients through the treatments or by cancer itself, and thus exacerbates the complications or the adverse effects from cancer treatments.[16] Especially oral mucositis, one of the major adverse effects from chemotherapy, leads to discomfort or pain, and consequently results in less food intake or susceptibility to infections.[17] Three elements of mucositis, anorexia and nutritional disorder correlate with each other, and compose the vicious circle of oral mucositis as an adverse effect by chemotherapy.[18]

In this study, subjective severity of oral mucositis in the Elental group was significantly lower than control group. This result illustrates that oral elemental diet improved the comfort level of cancer patients during chemotherapy, such as pain or dry mouth. The convalescence of the symptoms by oral mucositis would encourage the patients to continue the cancer treatments. Furthermore, the difference in the proportion of oral mucositis (grade ≥2) was more remarkable in the latter half of the treatment period, during which appetite often tends to decrease due to chemotherapy. This result supports the suggestion that elemental diet during chemotherapy can break the vicious circle of mucositis, including oral mucositis, diet disorder, and malnutrition.[18]

When concerning the maintenance of nutritional status in cancer patients, a well-balanced intake of amino acids plays a significant role.[19] Among amino acids, glutamine provides gut protection and can be a key factor of the suppressor to oral mucositis.[20,21] Hence, oral glutamine results in a moderate but significant reduction of mucositis in cancer patients during chemotherapy.[22] As Elental is rich in glutamine, it is probable that glutamine worked for the alleviation of oral mucositis in this study. However, the other amino acids are also the components of Elental, and the total correction of the nutrition status might be the major factor of the results. Further evaluation is needed to confirm the correlation with other elements, such as the blood concentration of glutamine during the treatment period.

To our knowledge, this is the first prospective study with randomized control trial, to investigate the effect of elemental diet on oral mucositis caused by chemotherapy. Oral mucositis still remains a quite difficult condition to manage under chemotherapy, and multidisciplinary approach with several methods is necessary for the prevention.[23] Based on the results of this study, elemental diet and nutritional support are also to be considered as a prophylaxis of oral mucositis. This is a preliminary report, and we plan to assess the effect of elemental diet further in a bigger sample size.

Our study has limitations in several respects. Findings from a small sample size are one of the limitations of the study. Larger prospective studies are needed to confirm the beneficial and adverse effects. This time a preliminary evaluation was conducted to assess the validity for the next large-scale study. The other limitation is that most patients in the Elental group did not receive the same dose of Elental. The dosage might have relevance to the results, and larger prospective studies are required for sure implications at this point as well.

In conclusion, the present randomized clinical trial illustrates the benefits of oral elemental diet in the prevention of oral mucositis when provided to cancer patients during chemotherapy. Future studies should be devoted to the optimization of the dose and regimen by using a larger group of patients.

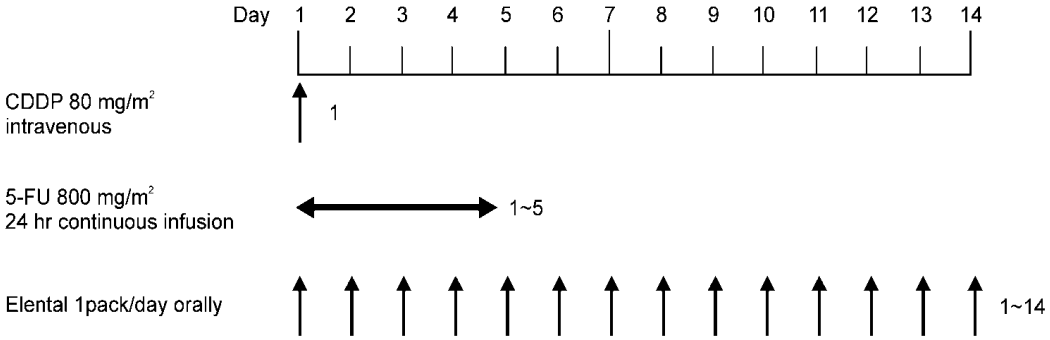
AUTHOR DISCLOSURES

None of the authors has any conflict of interest to declare. No funding was received for this work.

REFERENCES

1. Volpato LER, Silva TC, Oliveira TM, Sakai VT, Machado MA. Radiation therapy and chemotherapy-induced oral mucositis. Braz J Otorhinolaryngol. 2007;73:562-8. doi: 10.1016/S1808-8694(15)30110-5.
2. Childers NK, Stinnett EA, Wheeler P, Wright JT, Castleberry RP, Dasanayake AP. Oral complications in children with cancer. Oral Surg Oral Med Oral Pathol. 1993;75:41-7. doi: 10.1016/0030-4220(93)90404-R.
3. Sonis ST. Pathobiology of oral mucositis: novel insights and opportunities. J Support Oncol. 2007;5:3-11.
4. Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB. The burdens of cancer therapy: clinical

and economic outcomes of chemotherapy-induced mucositis. Cancer. 2003;98:1531-9. doi:10.1002/cncr.11671.
5. Riccardi D, Allen K. Nutritional management of patients with esophageal and esophagogastric junction cancer. Cancer Control. 1999;6:64-72.
6. Takeuchi H, Ikeuchi S, Kawaguchi Y, Kitagawa Y, Isobe Y, Kubochi K et al. Clinical significance of perioperative immunonutrition for patients with esophageal cancer. World J Surg. 2007;31:2160-7. doi: 10.1007/s00268-007-9219-8.
7. Daly JM, Weintraub FN, Shou J, Rosato EF, Lucia M. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. Ann Surg. 1995;221:327-38. doi: 10.1097/00000658-199504000-00002.
8. Yamamoto T, Shiraki M, Nakahigashi M, Umegae S, Matsumoto K. Enteral nutrition to suppress postoperative Crohn's disease recurrence: a five-year prospective cohort study. Int J Colorectal Dis. 2013;28:335-40. doi: 10.1007/s00384-012-1587-3.
9. Takagi S, Utsunomiya K, Kuriyama S, Yokoyama H, Takahashi S, Iwabuchi M et al. Effectiveness of an "half elemental diet" as maintenance therapy for Crohn's disease: a randomized-controlled trial. Aliment Pharmacol Ther. 2006; 24:1333-40. doi: 10.1111/j.1365-2036.2006.03120.x.
10. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, Epstein J et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004;100:2026-46. doi: 10.1002/cncr.20163.
11. Mahood DJ, Dose AM, Loprinzi CL, Veeder MH, Athmann LM, Therneau TM et al. Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. J Clin Oncol. 1991;9:449-52.
12. Cascinu S, Fedeli A, Fedeli SL, Catalano G. Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. Eur J Cancer B Oral Oncol. 1994;30B:234-6. doi: 10.1016/0964-1955(94)90003-5.
13. Ogata Y, Ishibashi N, Yamaguchi K, Uchida S, Kamei H, Nakayama G, Hirakawa H, Tanigawa M, Akagi Y. Preventive effects of amino-acid-rich elemental diet Elental® on chemotherapy-induced oral mucositis in patients with colorectal cancer: a prospective pilot study. Support Care Cancer. 2016:24:783-9. doi: 10.1007/s00520-015-2844-0.
14. Harada K, Ferdous T, Horinaga D, Uchida K, Mano T, Mishima K et al. Efficacy of elemental diet on prevention for chemoradiotherapy-induced oral mucositis in patients with oral squamous cell carcinoma. Support Care Cancer. 2016; 24:953-9. doi: 10.1007/s00520-015-2866-7.
15. Rivadeneira DE, Evoy D, Fahey TJ, Lieberman MD, Daly JM. Nutritional support of the cancer patient. CA Cancer J Clin. 1998;48:69-80. doi: 10.3322/canjclin.48.2.69.
16. Van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. Eur J Oncol Nurs. 2005;9: S51-63. doi:10.1016/j.ejon.2005.09.007.
17. Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol. 2001;19:2201-5.
18. Argilés JM. Cancer-associated malnutrition. Eur J Oncol Nurs. 2005;9:S39-50. doi:10.1016/j.ejon.2005.09.006.
19. Bozzetti F, Bozzetti V. Is the intravenous supplementation of amino acid to cancer patients adequate? A critical appraisal of literature. Clin Nutr. 2013;32:142-6. doi: 10.1016/j.clnu.2012.10.017.
20. Wischmeyer PE. Glutamine: role in gut protection in critical illness. Curr Opin Clin Nutr Metab Care. 2006;9:607-12. doi: 10.1097/01.mco.0000241672.09676.03.
21. Taniguchi M, Yano M, Tsujinaka T, Ogawa A, Morita S, Kaneko K et al. Parenteral nutrition decreases hepatic dihydropyrimidine dehydrogenase activity and modulates catabolism of 5-fluorouracil in rats. In Vivo. 2003;17:219-23.
22. Curi R, Lagranha CJ, Doi SQ, Sellitti DF, Procopio J, Pithon-Curi TC et al. Molecular mechanisms of glutamine action. J Cell Physiol. 2005;204:392-401. doi: 10.1002/jcp.20339.
23. Sharma R, Tobin P, Clarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea. Lancet Oncol. 2005;6:93-102. doi: 10.1016/S1470-2045(05)01735-3.



Supplementary figure 1. Treatment schedule, CDDP, cisplatin; 5-FU, 5-fluorouracil

Supplementary table 1. Composition of Elental

Total	1 pack/80 g (300 kcal)	Amino acids	14.1 g
Amino acids	14.1 g	L-Isoleucine	642 mg
Carbohydrate (dextrin)	63.4 g	L-Leucine	899 mg
Lipid (soybean oil)	0.51 g	L-Lysine-HCl	888 mg
Vitamin A	648 IU	L-Methionine	648 mg
Vitamin D	51.2 IU	L-Phenylalanine	871 mg
Vitamin B-1	0.15 mg	L-Thereonine	523 mg
Vitamin B-2	0.24 mg	L-Tryptophan	151 mg
Vitamin B-6	0.22 mg	L-Valine	701 mg
Niacin	2.20 mg	L-Histidine-HCl-H2O	501 mg
Pantotenic acid	1.10 mg	L-Arginine-HCl	1125 mg
Folic acid	44 μg	L-Alanine	899 mg
Vitamin B-12	0.72 μg	Mg-K-L-Aspartate	1036 mg
Vitamin C	7.80 mg	Na-L-Aspartate-H2O	867 mg
Vitamin K	9 μg	L-Glutamine	1932 mg
Vitamin E	3.3 IU	Glycine	505 mg
Biotin	39 μg	L-Proline	630 mg
Choline	8.56 mg	L-Serine	1159 mg
Na	260 mg	L-Tyrosine	110 mg
K	217 mg		
Cl	517 mg		
Mg	40 mg		
Ca	158 mg		
P	122 mg		
Fe	1.8 mg		
I	15.2 μg		
Mn	0.3 mg		
Cu	0.2 mg		
Zn	1.8 mg		

Name	

day		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Elental One pack(80 g)/day		↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Elental One pack(80 g) /day	Intake	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Whole
		2/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3
		Half	Half	Half	Half	Half	Half	Half	Half	Half	Half	Half	Half	Half	Half
		1/3	1/3	1/3	1/3	1/3	1/3	1/3	1/3	1/3	1/3	1/3	1/3	1/3	1/3
		None	None	None	None	None	None	None	None	None	None	None	None	None	None
	Form	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly	Liquid jelly
Content of meals															
Eating rate															
Oral mucositis															
Diarrhea															

	1	2	3
Oral mucositis	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake	Severe pain; interfering with oral intake
Diarrhea	Increase of 1-3 stools per day over usual	Increase of 4-6 stools per day over usual	Increase of >=7 stools per day over usual

特記事項

Supplementary figure 2. Questionnaire sheet