The amino acid-rich elemental diet Elental® preserves lean body mass during chemo- or chemoradiotherapy for esophageal cancer

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Abstract. Chemo (chemoradio) therapy can induce oral mucositis and change body composition in patients with esophageal cancer. The impact of the amino acid-rich elemental diet Elental® on oral mucositis and changes in body composition during chemo (chemoradio) therapy is unclear. Thus, the purpose of the present study was to examine the preventive effects of Elental on oral mucositis and sarcopenia progression during chemo (chemoradio) therapy for esophageal cancer. Patients were randomized to receive either azulene oral rinse (Arm 1) or Elental (Arm 2) during the treatment cycle (4 weeks). The incidence of oral mucositis and other adverse events was evaluated weekly. Body composition pre- and post-treatment cycle was measured by bioelectric impedance analysis. Thirty-three patients (17 azulene and 16 Elental) completed the study, and the groups were well matched. Elental tended to reduce the incidence of oral mucositis (Arm 1, 23.5% and Arm 2, 12.5%), but there was no statistically significant difference between the groups. The average body mass index (BMI) and body fat mass decreased significantly in both groups after the treatments. Lean body mass (LBM) was reduced in Arm 1, but was increased in Arm 2 after the treatment; the relative change of LBM after the treatment was significant between Arm 1 and Arm 2 (P=0.007). This study revealed that Elental nutrition could counteract sarcopenia development during chemoradiotherapy for esophageal cancer. These properties may lead to improvement of the quality of life and clinical outcome of esophageal cancer patients treated with chemo (chemoradio) therapy (Clinical Trial Registry ID: UMIN 000007960).

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Abbreviations: BMI, body mass index; LBM, lean body mass; ECOG, Eastern Cooperative Oncology Group; CTCAE, the Common Terminology Criteria for Adverse Events; SMI, skeletal muscle index; DAO, diamine oxidase; BCAA, branched-chain amino acids

Key words: sarcopenia, oral mucositis, elemental diet, chemotherapy, esophageal cancer

Introduction

Aggressive cancer therapy including chemo- and chemoradiotherapy can help patients with various malignancies to achieve greater improvement in survival and prognosis. However, these therapies frequently cause some serious adverse events. Of these, oral mucositis is one of the most frequent and clinically significant complications induced by chemotherapy, with or without radiotherapy (1). Serious oral mucositis, which involves both erythema and painful mucosal ulceration, can cause difficulty in swallowing, dehydration, malnutrition and increased risk for infection (2,3). These clinical sequelae can limit the tolerated dose of chemotherapy, leading to poor prognosis, and severely impair the health-related quality of life (3,4). It has been reported that the incidence of oral mucositis induced by conventional chemotherapy for esophageal cancer is relatively high (35-60%) and that the DCF regimen (docetaxel, cisplatin and 5-fluorouracil), which is occasionally used for patients with esophageal cancer in Japan, is one of the high-risk regimens for oral mucositis (3,5-7). Unfortunately, there are few agents that have been confirmed to reveal consistent protective action against chemo (chemoradio) therapy-induced oral mucositis to date.

Involuntary weight loss is considered a hallmark of advanced cancer, and esophageal cancer has been reported to have the highest median percentage weight loss among the primary tumor sites evaluated (8). Cancer cachexia leads to body weight loss by reducing both lean and fat mass, and muscle loss has recently emerged as a more serious concern. Sarcopenia, which was initially defined as the loss of skeletal muscle mass that occurs with aging, has also been recognized as a clinically important phenomenon that is associated with reduced quality of life and poor clinical outcome in

malignant conditions (9,10). There is mounting evidence that sarcopenia or sarcopenic obese patients are independently associated with a poor response to cancer therapy in various malignancies, such as melanoma (11), renal cell (12), hepatic carcinoma (13), colorectal (14), pancreatic (15), breast (16) and lung cancer (17). However, there is limited knowledge on the impact of sarcopenia on the prognostic value and response to chemo (chemoradio) therapy for esophageal cancer. A recent study demonstrated that body composition was markedly changed following chemotherapy for esophageal cancer, and a significant reduction of fat free mass (skeletal muscle) was observed during chemotherapy and the incidence of sarcopenia increased from 57% before chemotherapy to 78.7% after completion of chemotherapy (18). Counteraction of sarcopenia progression during chemotherapy in some way (e.g. nutritional supplement) is considered to be important, since it may attenuate the toxicity of anticancer agents and improve the therapeutic efficacy of chemo (chemoradio) therapy. Although supplementation has been suggested as means of attenuating the reduction of fat free mass during chemotherapy (19,20), robust data supporting that supplemental intervention in cancer patients improves sarcopenia progression during chemo (chemoradio) therapy are currently lacking.

Elental® is one of the widely used nutritional supplements and its special formula contains a variety of amino acids, together with easily digestible nutritions, minerals, vitamins and a major energy source, dextrin (Table I). Fat is present in a very small amount, whereas L-glutamine is present at an especially high dose (1.932 mg/package). Several reports have demonstrated that glutamine supplementation decreases the incidence and severity of chemo (chemoradio) therapy-induced mucositis (21-23). Moreover, it has been reported that amino acids, such as leucine, can stimulate muscle protein synthesis (24) and that supplementation of amino acids improves or prevents sarcopenia in several diseases, including cancer (25). These observations led us to examine the preventive effects of Elental on oral mucositis and sarcopenia progression during chemo (chemoradio) therapy for esophageal cancer.

The primary endpoint of this trial was to explore the potential preventive effect of the amino acid-rich elemental diet Elental on chemo (chemoradio) therapy-induced oral mucositis in patients with esophageal cancer. The impact of the anticatabolic properties of Elental was also studied as a secondary endpoint. Herein, we report that Elental nutrition could counteract sarcopenia progression during chemo (chemoradio) therapy for esophageal cancer, but we did not demonstrate efficacy against chemo (chemoradio) therapy-induced oral mucositis.

Materials and methods

Patients. Participants with pathologically diagnosed primary squamous cell carcinoma of the esophagus who were scheduled to undergo chemotherapy or chemoradiotherapy were recruited. They fulfilled the following eligibility criteria: age between 20 to 80 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; at least six months since the last chemotherapy or radiation therapy; and adequate hematologic, hepatic, renal and cardiac function.

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

Composition	Amount
Energy (kcal)	300
Carbohydrate (g)	
Dextrin	63.41
Fat (g)	
Soy bean oil	0.51
Amino acid (g)	14.1
Amino acid (mg)	
L-Isoleucine	642
L-Leucine	899
Lysine hydrochloride	888
L-Methionine	648
L-Phenylalanine	871
L-Threonine	523
L-Tryptophan	151
L-Valine	701
L-Histidine hydrochloride monohydrate	501
L-Arginine hydrochloride	1,125
L-Alanine	899
L-Aspartic acid magnesium potassium	1,036
L-Aspartic acid sodium monohydrate	867
L-Glutamine	1,932
Aminoacetic acid	505
L-Proline	630
L-Serine	1,159
L-Tyrosine	110
BCAA (mg)	2,242
BCAA branched-chain amino acids	

The exclusion criteria were: presence of uncontrolled infection; presence of severe gastrointestinal stenosis or bleeding; requirement for total parental nutrition; the use of other nutritional supplements; poor control of diabetes or the use of insulin treatment.

Study design. This was a randomized, open label, phase 2 clinical trial with patients randomized in a 1:1 allocation to one of two arms: Arm 1 (control arm), azulene (Azunol® Gargle liquid 4%; Nippon Shinyaku Co., Kyoto, Japan) oral rinse; Arm 2, the elemental diet Elental®. Azulene was used as a control agent since this compound is approved for oral mucositis therapy in Japan. Randomization was stratified by treatment (chemotherapy/chemoradiotherapy) and stage using a stratified permuted block-randomization scheme. Azulene oral rinse was prepared by pouring 5 drops of 4% liquid solution into 100 ml of water. At the start of chemo (chemoradio) therapy, patients underwent oral rinsing with azulene solution 3 times a day until the end of the treatment course. Elental was administered at 80 g (one package)/day to patients in Arm 2 from the start of the treatment until the end of the treatment course. The composition of Elental is shown in the Table I.

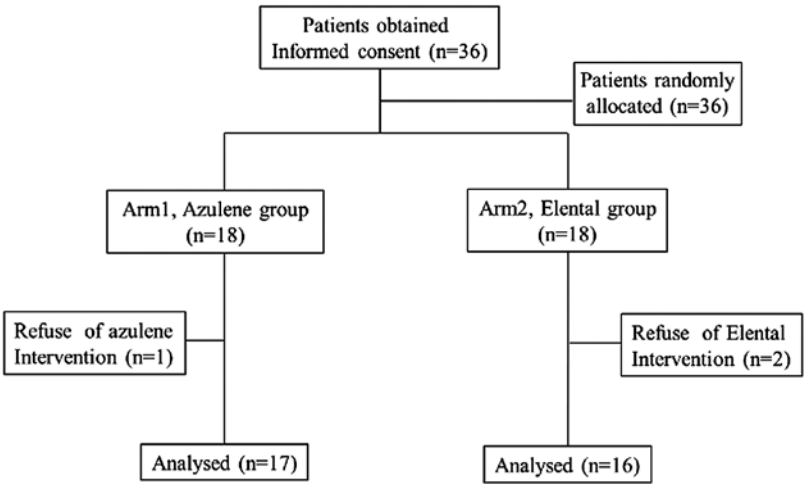

Figure 1. Consort diagram.

The primary objective of the present study was to estimate the incidence and severity of oral mucositis during one cycle of treatment (4 weeks). Changes of nutrition indicators (e.g. serum total protein, albumin, hemoglobin and body composition) during chemo (chemoradio) therapy were also evaluated as secondary objectives. The present study was approved by the ethics committee of Kyoto Prefectural University of Medicine. The trial was designed and conducted in accordance with the Helsinki Declaration and the Ethical Guidelines for Clinical Research (the Ministry of Health, Labor and Welfare, Japan). All participants provided written informed consent. This trial was registered as the University Hospital Medical Information Network (UMIN) Clinical Trial Registry as ID: UMIN 000007960.

Assessment

Evaluation of oral mucositis and other adverse events. The incidence of oral mucositis was evaluated and the severity of all side-effects was graded by one researcher according to the Common Terminology Criteria for Adverse Events v.4.0 (CTCAE). Oral pain was assessed using a numerical rating scale (NRS). The side-effects were checked every week and the worst score obtained during the observation period (4 weeks after commencing the treatment) was included in the data for comparison.

Nutritional status assessment

Body composition measurement. Body composition was assessed at the initiation of the chemo (chemoradio) therapy and ~4 weeks after commencing the treatment, using multifrequency bioelectrical impedance with eight tactile electrodes (InBody 720; Biospace Co., Ltd., Seoul, Korea). With this method, body weight, body mass index (BMI), body fat mass and lean body mass (LBM) were measured automatically and simultaneously. The InBody has been reported to be an accurate substitute for dual-energy X-ray absorptiometry (DXA) for the measurement of body composition (26). The skeletal muscle index (SMI) (kg/m^2) is calculated as the appendicular skeletal muscle mass divided by the square of the height. In the present study, cut-off values for sarcopenia were based on the consensus report from the Asian Working Group for Sarcopenia (AWGS) (27); (i.e., SMI: <7.0 kg/m^2 for men and 5.7 kg/m^2 for women using bioimpedance analysis).

Blood test. Blood tests, such as serum total protein, albumin, blood hemoglobin, C-reactive protein (CRP), erythrocyte, white blood cell, neutrophil and lymphocyte counts were determined routinely. Outcomes were assessed at the initiation of the chemo (chemoradio) therapy and 4 weeks after commencing the treatment.

Statistical analysis. Patients who received at least one dose of azulene or Elental were included in the analyses. Based on the results of previous studies (28-30), the difference between the incidences of oral mucositis for two arms was assumed to be 35% (the incidence for the azulene arm and Elental Arm being 50 and 15%, respectively). With one-sided type I error=0.1 and type II error=0.2, it was necessary to include 16 patients in each arm. Assuming 10% drop-out, we calculated that a total of 18 patients were required in both treatment arms. The baseline characteristics of the patients were compared between the treatment arms using Chi-squared test (applying the Yates correction when necessary) for categorical variables and using Student's t-test for continuous variables. Differences between paired observations were determined using the Student's paired t-test. P-values <0.05 were considered significant. All statistical analyses were performed with GraphPad Prism 5 for Windows (Graphpad Software, Inc., San Diego, CA, USA).

Results

Patient characteristics. Thirty-six patients were enrolled in the study between February 2012 and April 2015, after signing the written informed consent, and they were randomly assigned to receive oral rinse with azulene (Arm 1, n=18) or to undergo administration of Elental® (Arm 2, n=18). Of them, three patients were excluded from analysis (Arm 1, 1; Arm 2, 2), who did not receive either treatment (i.e., azulene or elental). Consequently, 33 patients were included in the complete analysis (Fig. 1). The average BMI and SMI for the 33 patients was 20.42 and 6.59 kg/m^2, respectively. Although sarcopenia was observed in 20 patients (60.6%) prior to treatment, there

Table II. Baseline patient characteristics.

Characteristics	Arm 1 (Azulene, n=17)	Arm 2 (Elental, n=16)	P-value
Gender (Male/female)	13/4	14/2	1
Age, median (range)	66 (44-79)	68 (50-76)	0.46
ECOG performance status			
0	8	6	0.51
1	9	10	
Stage			
I	3	4	0.95
II	1	1	
III	9	7	
IV	4	4	
Treatment			
Chemotherapy (doublet/triplet)	9 (7/2)	8 (4/4)	1
Chemo-radiotherapy	8	8	
BMI (kg/m^2)	20.39±2.84	20.46±1.76	0.93
Body fat weight (kg)	12.08±5.65	12.39±3.20	0.85
LBM (kg)	23.78±0.94	24.35±1.06	0.69
SMI (kg/m^2)	6.57±0.85	6.60±0.74	0.92
Albumin (g/dl)	3.78±0.38	3.78±0.37	0.99
Total cholesterol (mg/dl)	187.1±41.8	193.6±28.6	0.63
CRP (mg/dl)	0.16 (0.02-5.32)	0.43 (0.02-8.66)	0.24
White blood cell count (/mm^3)	5706±1756	7169±3293	0.12
Total neutrophil count (/mm^3)	3408±1695	4694±3035	0.14
Total lymphocyte count (/mm^3)	1719±478	1658±574	0.74
Hemoglobin (g/dl)	12.9±1.14	13.0±1.75	0.84

ECOG, The Eastern Cooperative Oncology Group; BMI, body mass index; LBM, lean body mass; SMI, skeletal muscle index; CRP, C-reactive protein.

Table III. Maximum severity of oral mucositis.

	Patients, n (%)		
Maximum grade	Arm 1 (Azulene, n=17)	Arm 2 (Elental, n=16)	P-value
1	13 (76.5)	14 (87.5)	
2	4 (23.5)	1 (6.25)	0.246
3	0 (0)	1 (6.25)	

Table IV. Maximum severity of oral pain.

	Patients, n (%)		
Maximum severity grade of oral pain	Arm 1 (Azulene, n=17)	Arm 2 (Elental, n=16)	P-value
0	12 (70.6)	12 (75)	0.728
1	3 (17.6)	1 (6.25)	
2	1 (5.9)	2 (12.5)	
≥3	1 (5.9)	1 (6.25)	

was no sarcopenic obesity, i.e., sarcopenia combined with BMI ≥25 kg/m^2. The baseline patient characteristics were similar between the groups (Table II). As randomization was stratified by treatment (chemotherapy/chemoradiotherapy) and stage, these were well balanced between the treatment groups. However, with respect to the chemotherapy regimen, triplet chemotherapy regimen, which is a more toxic regimen with an increased incidence of stomatitis (31), was more frequently used for patients in Arm 2 (Arm 1=22.2%; Arm 2=50.0%). Although CRP (P=0.24), white blood cell count (P=0.12) and total neutrophil count (P=0.14) tended to be higher in patients in Arm 2, the differences were not statistically significant. BMI and body composition (i.e., body fat mass and LBM) were comparable between the groups.

Incidence and severity of oral mucositis. During the treatment cycle, oral mucositis CTCAE grade ≥2 developed in 6 patients (18.2%). The incidence of oral mucositis grade ≥2 tended to be lower for patients treated with Elental (Arm 1=23.5%;

Table V. Adverse events according to treatment group.

	Arm 1 (Azulene, n=17)				Arm 2 (Elental, n=16)			
Toxicity	Grade1	Grade 2	Grade 3	Grade 4	Grade1	Grade 2	Grade 3	Grade 4
Hematological								
Leukopenia	0	5	4	2	3	3	3	1
Neutropenia	0	2	3	4	0	1	2	2
Lymphocytopenia	2	5	6	0	3	4	7	0
Anemia	11	2	0	0	9	4	0	0
Thrombocytopenia	6	3	0	1	6	1	0	0
Elevated AST	3	0	0	0	4	0	0	0
Elevated ALT	6	1	0	0	8	0	0	0
Non-hematological								
Fatigue	8	5	0	0	6	1	0	0
Anorexia	3	12	0	0	2	8	1	0
Nausea	4	8	0	0	5	1	0	0
Diarrhea	2	0	0	0	4	1	0	0
Constipation	13	0	0	0	10	0	0	0

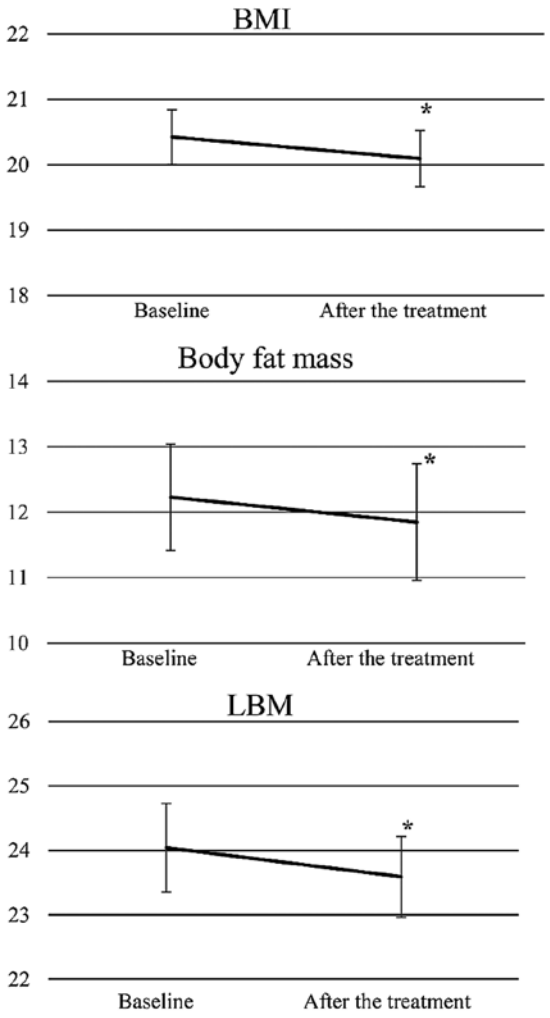

Figure 2. Changes in body composition after the treatment relative to the baseline. The average BMI, body fat mass and LBM in 33 patients decreased significantly after the treatment relative to the baseline. Data are expressed as the mean ± SEM. *P<0.05. BMI, body mass index; LBM, lean body mass

Arm 2=12.5%), but this was not statistically significant (Table III). Analysis of the severity of oral pain is shown in Table IV. Most of the patients (72.7%) did not complain of oral pain and oral pain grade ≥2 was observed in only 5 patients (15.2%). There was no significant difference in the maximum severity of oral pain between Arm 1 (azulene) and Arm 2 (Elental).

Changes of nutrition indicators from baseline. The average BMI, body fat mass and LBM in the 33 patients decreased significantly after chemo (chemoradio) therapy (Fig. 2). Relative changes of nutrition indicators after the treatment from baseline were calculated using the following formula: 100 x (value after-value before)/value before. When the relative changes of nutrition indicators were compared between Arm 1 (azulene) and Arm 2 (Elental) groups (Fig. 3), a different pattern appeared when BMI, body fat mass and LBM were expressed as the percent change from baseline for each group. BMI and body fat mass were reduced after the treatment relative to baseline in both groups. By contrast, LBM was lost in Arm 1, but increased in Arm 2 after the treatment compared with the baseline values. There was a significant difference between the change of LBM in Arm 1 and in Arm 2 (P=0.007). The laboratory values for total protein, albumin and hemoglobin decreased but total cholesterol increased in both groups after treatment. The relative change of total cholesterol increased more in Arm 1 than in Arm 2, but there was no statistically significant difference between the two groups (P=0.33).

Adverse events of chemotherapy. With respect to adverse events other than oral mucositis during the treatment cycle, common grade 3/4 toxicities included leukopenia, neutropenia and lymphocytopenia (Table V). Although the grade 3/4 neutropenia occurred more often in Arm 1 compared with Arm 2 (41.2 and 25.0%, respectively), this was not statistically

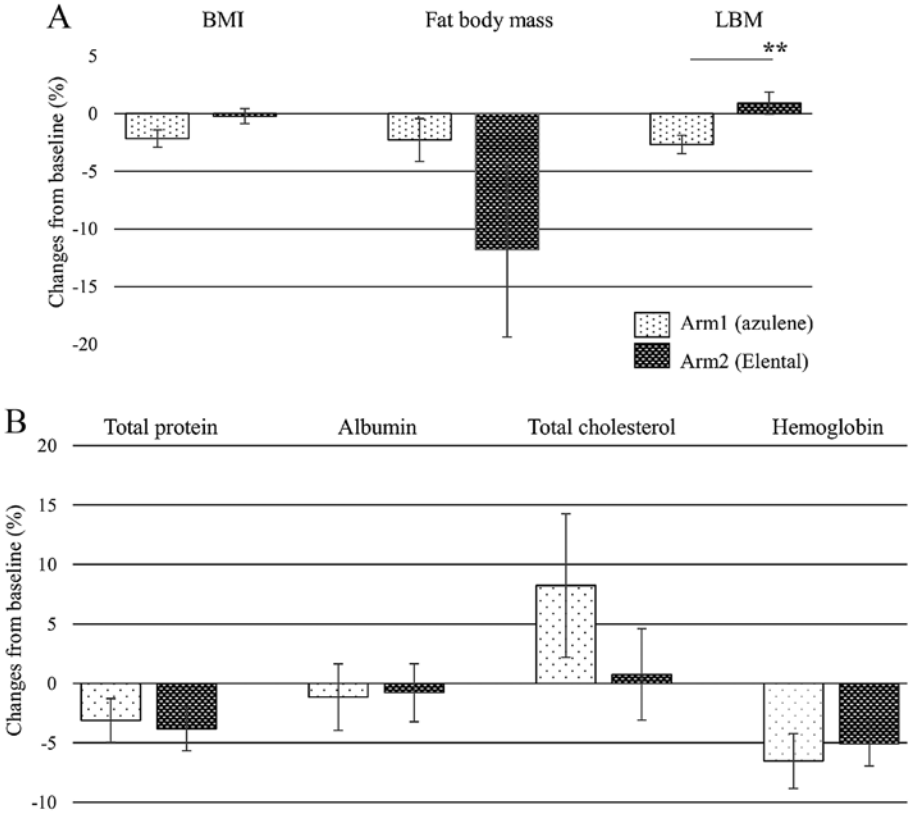

Figure 3. Comparison of the relative changes from baseline in nutritional indicators between treatment groups. (A) Body composition (BMI, fat body mass and LBM). (B) Serum total protein, albumin, total cholesterol and hemoglobin. LBM increased in Arm 2 after the treatment, but decreased in Arm 1; this difference was significant. With respect to the other indicators, there were no statistically significant differences between groups. Data are expressed as the mean ± SEM. **P<0.01. BMI, body mass index; LBM, lean body mass.

significant (P=0.46). The incidence of diarrhea was greater in Arm 2 than in Arm 1 (31.3 and 11.8%, respectively), and was grade 2 or less. There were no statistically significant differences in the incidence or severity of hematological and non-hematological adverse effects between the two arms.

Discussion

Profound weight loss and malnutrition subsequent to severe dysphagia and cancer cachexia are cardinal symptoms in esophageal cancer. Recently, it has been reported that ~25-55% of patients with esophageal cancer undergoing neo-adjuvant therapy were sarcopenic at the time of diagnosis (18,32-35). Moreover, two recent studies in esophageal cancer patients have shown that muscle wasting can worsen with cancer chemo- or chemoradiotherapy (18,34). Although the primary endpoint of a preventive effect against oral mucositis was not met, the present study demonstrated several noteworthy findings. First, the overall prevalence of sarcopenia among Japanese esophageal cancer patients was 60.6% in the present study, which is higher than the prevalences described in previous reports for esophageal cancer patients mainly from Europe (18,32-35). On the other hand, sarcopenic obesity was not observed in this study, however, Anandavadivelan *et al* (32) reported sarcopenic obesity in 14% of esophageal cancer patients in Sweden. Second, in most patients, both body fat mass and LBM were reduced during the treatment cycle, and average values among all participants were decreased significantly after chemo (chemoradio) therapy. Third, the most important finding in this study is that enteral nutrition using Elental could maintain or even increase LBM post chemo (chemoradio) therapy.

Sarcopenia was recently identified as a poor prognostic factor in patients with various malignancies, such as melanoma, hepatic carcinoma, pancreatic and lung cancer, and liver metastasis from colorectal cancer (11,13,15,17,36). Moreover, sarcopenia and sarcopenic obesity are associated independently with a poor response to cancer chemotherapy in melanoma (11), renal-cell (12), hepatic carcinoma (13), colorectal (14), pancreatic (15), breast (16) and lung cancer (17). More recently, sarcopenic obesity has been reported to be a probable risk factor for dose limiting toxicity during chemotherapy for esophageal cancer (32). Thus, it has become apparent that sarcopenia has a clinically significant impact on treatment response and survival in various malignancies, including esophageal cancer.

The rate of malnutrition in patients with esophageal cancer has been estimated to be as high as 78.9% (37) and marked reductions in both body fat mass and skeletal muscle mass occur during chemotherapy for esophageal cancer (18). Nutritional support is important to decrease major post-operative complications in esophageal cancer patients (38,39). However, the significance of nutritional intervention in patients undergoing chemo- or chemoradiotherapy for esophageal cancer is not clear. In the present study, LBM decreased during treatment in the azulene (control) group, but increased in the Elental® group relative to the baseline and there was

a significant difference between the two groups. To the best of our knowledge, this is the first report demonstrating that nutritional intervention can counteract skeletal muscle wasting during chemo- or chemoradiotherapy for esophageal cancer. The treatment response to chemo (chemoradio) therapy did not differ between the azulene and Elental groups in the present study (average change in tumor size after 1 cycle treatment; -18.4 vs. -18.1%, respectively; data not shown), however, this may be due to the short observation period. We believe that nutritional intervention during cancer treatment is important, and can contribute to the improvement of both malnutrition as well as the clinical outcome in cancer patients. Further studies over a longer follow-up period of time are needed to confirm these observations.

It has been reported that amino acid supplementation can stimulate muscle protein synthesis (24,40,41), and among the amino acids, leucine has been recognized to play a significant role in muscle protein synthesis (42). Elental, which does not contain a great amount of leucine (6.84%) (Table I), does contain a large amount of amino acids (12.66 g/one pack). In considering the possible explanations for the results of this study, it appears likely that muscle protein synthesis was enhanced by the high amount of amino acids contained in Elental. Another possible explanation is that Elental could help to maintain mucosal integrity in the gastrointestinal tract, thereby resulting in maintained nutrient absorption. Anticancer drugs, such as 5-fluorouracil, can induce small intestinal mucosal injury and plasma diamine oxidase (DAO) has been reported to be a useful indicator of mucosal injury of the gastrointestinal tract (43). Tanaka *et al* (7) recently reported that plasma DAO activity was decreased after chemotherapy in patients with esophageal cancer, and patients treated with the Elental diet exhibited a significant increase in DAO activity after chemotherapy. While we did not measure plasma DAO activity during chemo (chemoradio) therapy, amino acids, such as glutamine, which is abundant in Elental, could prevent anticancer drug-induced intestinal mucosal injury and maintain nutrient absorption, including the amino acids, thus contributing to stimulate muscle protein synthesis. However, plasma amino acid concentrations were not measured during this study, and doing this in future experiments could help to validate the results presented here. We also believe further experimental studies are needed to confirm the underlying mechanism.

The present study did not provide evidence of the effectiveness of Elental in protecting against the development of oral mucositis during chemo (chemoradio) therapy. The incidence of oral mucositis (≥ grade 2) in this study was 18.2% among all enrolled patients, which was much lower than previously assumed (the incidence for the azulene arm being 50%), which makes it difficult to achieve statistical significance. Despite lacking statistical significance, the incidence of oral mucositis in the Elental arm was lower than that in the azulene arm (12.5 vs. 23.5%, respectively). It is possible that evidence supporting the efficacy for Elental against oral mucositis might be achieved, if the study were to focus on a high-risk population susceptible to oral mucositis, such as patients who have experienced it prior to undergoing chemo (chemoradio) therapy.

In conclusion, this study revealed that Elental could counteract the development of sarcopenia during the treatment cycle, though we could not demonstrate the efficacy of Elental against chemo (chemoradio) therapy-induced oral mucositis in esophageal cancer patients. Further clinical studies with a larger sample size should be conducted to confirm these results and to elucidate whether the preventive effect of Elental against sarcopenia leads to an improvement of the clinical outcome of esophageal cancer patients undergoing treatment with chemo (chemoradio) therapy.

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