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ORIGINAL ARTICLE

Preventive effects of amino-acid-rich elemental diet Elental® on chemotherapy-induced oral mucositis in patients with colorectal cancer: a prospective pilot study

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Abstract
Purpose The prospective pilot study was designed to evaluate the preventive effects of amino-acid-rich elemental diet (ED), Elental®, on chemotherapy-induced oral mucositis in patients with colorectal cancer. The factors influencing its efficacy are also investigated.
Methods A total of 22 eligible patients with colorectal cancer experiencing grade 1–3 oral mucositis during treatment with fluorouracil-based chemotherapy entered the current study. Their average age was 67 years. There were 10 male and 12 female. The PS was 0 in the majority of patients. Patients received two courses of the same chemotherapy regimen and Elental® concurrently after recovery to grade 0 or 1 oral mucositis.
Results FOLFOX6 + bevacizumab in 8 patients, FOLFIRI + bevacizumab in 8 patients, FOLFIRI + panitumumab in 1 patient, FOLFIRI in 1 patient, XELOX + bevacizumab in 2 patients, and S-1 + cetuximab in 2 patients were used as first-line (16 cases) or as second-line (6 cases) chemotherapy. Dose reduction of 5-fluorouracil (5-FU) or oral fluoropyrimidine was performed in the 2 patients achieving grade 3 oral mucositis and in the 3 patients achieving grade 2 oral mucositis. The maximum grade of oral mucositis decreased in 18 of the 22 patients during the first treatment course with Elental® ($p = 0.0002$) and in 20 of the 22 patients in the second course ($p < 0.0001$). Multivariate analyses found that the dose reduction in 5-FU or oral fluoropyrimidine, ED intake, and the prior administration of ED were each a significant factor for the preventive efficacy on oral mucositis.
Conclusion The amino-acid-rich elemental diet Elental® may be useful as a countermeasure for 5-FU-based chemotherapy-induced oral mucositis in patients with colorectal cancer.

Keywords Chemotherapy · Oral mucositis · Elemental diet (ED) · Nourishment academic intervention · Colorectal cancer · Amino acid

Introduction

Mucositis is a common adverse effect of chemotherapy and/or radiotherapy. The oral mucositis that is the mouth mucous membrane injury causes anguish to the patient regardless of the severity of symptoms and induces a decrease in quality of life (QOL) and in desire for continuation of the treatment. After oral mucositis once occurs, adjustments must be made to the dose of the anticancer drug and to the administration schedule, as well as requiring new preventive care to the mouth [1]. Therefore, to continue chemotherapy as far as possible without decreasing the dose, some effective oral mucositis preventive measures are needed.

The mechanism of chemotherapy-induced mucositis has been described as occurring stepwise through a sequence of events [2]. First, chemotherapy causes direct DNA damage resulting in the death of basal epithelial cells and the generation of reactive oxygen species (ROS) that damage connective tissue, DNA, and cell membranes. Second, this cell damage causes the activation of several transcription factors including nuclear factor-kappa B (NF-κB), wnt, and p53, and their molecular pathways. Third, these pathways are further amplified

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via positive feedback loops. Finally, cell death causes mucosal thinning, resulting in the development of clinical and symptomatic ulcerated mucositis. The generation of the oral mucositis appears at around 5 to 10 days after the initiation of chemotherapy in relation to the cell cycle of the mouth mucous membrane epithelial cells. After the appearance of the mucous membrane injury, 2 to 3 weeks are required to achieve recovery, since the usual regeneration cycle of the oral mucosa is around 7 to 14 days. The period until recovery, the frequency, and the severity of oral mucositis each depends on the kind and the dose of the anticancer drug, the treatment regimen, and the general condition of the patient.

The incidence of oral mucositis, induced by colorectal cancer chemotherapy such as FOLFOX and FOLFIRI including bolus and continued infusion of 5-fluorouracil (5-FU), and XELOX that uses oral 5-FU, is high at 25–40 % [3–5]. Glutamine is a natural amino acid which functions as a substrate for nucleotide synthesis in most dividing cells [6]. There have been several randomized studies to date on the use of glutamine in chemotherapy- and radiotherapy-induced mucositis with varying results [7, 8]. Another study, focused on the action of mucous protection of the glutamine [9] in addition to the countermeasures for oral intake trouble, suggests a prospective pilot study to evaluate preventive effects of the elemental diet (ED) Elental®, (one packing 80 g/300 kcal) which contains 1932 mg of L-glutamine, on oral mucositis caused by chemotherapy. Elental® is composed of various amino acids, very little fat, vitamins, trace elements, and a major energy source, dextrin. The composition of Elental® is detailed elsewhere [10]. In the present study, the preventive effects of the ED on oral mucositis and the factors influencing its efficacy are followed prospectively, and the significance of such nourishment intervention as a countermeasure is discussed.

Patients and methods

Eligibility criteria

A total of 23 metastatic colorectal cancer patients were registered prospectively after developing grade 1–3 oral mucositis between September 2008 and December 2010 during 5-FU-based chemotherapy involving mFOLFOX6, FOLFIRI, XELOX, or S-1 with or without biologics. Each of these eligible patients had histologically confirmed advanced or metastatic cancer. No patient had received prior radiotherapy or concurrent radiotherapy. The criteria for entry into our study included age older than 20 years, Eastern Cooperative Oncologic Group (ECOG) performance status ≤2, neutrophils ≥1500/mm^3, platelets ≥750,000/mm^3, creatinine ≤1.5 times the upper normal limit or creatinine clearance of more than 60 mL/min, and liver function tests (serum bilirubin level ≤1.5 times the upper normal limit and AST/ALT <3 times the upper normal limit). All patients were required to be free of any signs of systemic infection and must not have taken antibiotics. Each patient gave written informed consent before entering the study. The study was performed in accordance with the Declaration of Helsinki.

Administration of Elental® and anticancer drugs

Two courses of the same chemotherapy that induced the oral mucositis were performed with or without dose reduction in 5-FU or oral fluoropyrimidine. The chemotherapy was then restarted according to the standard criteria of clinical trials such as neutrophil depletions of grade 1 or less and decrease in platelet of grade 1 or less as the hematological toxicity, and oral mucositis of grade 1 or less, peripheral neurological symptoms of grade 1 or less, protein urea and hemorrhage of grade 1 or less, and diarrhea of grade 1 or less as the non-hematological toxicity. In those patients experiencing grade 3 oral mucositis and in those patients experiencing grade 2 oral mucositis which persisted even after 7 days of next chemotherapy delay, the chemotherapy was restarted with a dose reduction in 5-FU/oral fluoropyrimidine after all oral mucositis recovered to grade 1 or less. The ED Elental® (80 g/300 kcal or more per day) was given perorally in addition to normal oral ingestion, together with chemotherapy in each course lasting 2 to 3 weeks (on days 1–14 or days 1–21). To help the patient, the ED was flavored and made into a jelly. Patients recorded the daily Elental® intake and the chief physician collected the data before the next course of chemotherapy.

Oral mucositis assessment

Chemotherapy-induced oral mucositis was graded basically according to version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE v3.0). The CTCAE v3.0 grades were defined as follows: grade 0, no mucositis; grade 1, minimal symptoms such as pain/throat pain and erythema of the mucosa; grade 2, obviously symptomatic but can eat, patchy ulceration, or pseudomembranes; grade 3, obviously symptomatic and cannot eat, confluent ulceration, or pseudomembranes, and bleeding with minor trauma; and grade 4, severely symptomatic in association with life-threatening consequences, tissue necrosis, and/or with significant spontaneous bleeding. Patients daily recorded mouth and throat soreness and activity score that was modified from the Oral Mucositis Daily Questionnaire (OMDQ) (questions 2 and 3) [11]. Finally, oral mucositis was assessed by independent physician based on the patient's self-assessment of the mouth and throat soreness and activity score, the pre-treatment patient interview by pharmacologists and chief physician's decision every week on out-patient basis for

the study period. The maximum grade of oral mucositis at individual chemotherapy course were recorded by the independent physician.

Endpoints and statistical methods

The ED intake in each course, the presence and grade of the oral mucositis, and the presence and grade of any adverse effect were monitored. Multivariate analysis for the factors (age, gender, PS 0 vs. 1–2, usage of antiepidermal growth factor receptor (EGFR) antibodies, pretreatment albumin value, pretreatment lymphocyte, number of anticancer drugs 2 vs. 3, regimen duration 2 vs. 3 weeks, treatment phase: first line vs. second line, improvement in neutrophil depletion, ED intake, prior treatment with ED, dose reduction in 5-FU or oral fluoropyrimidine) related to the efficacy of the ED on oral mucositis was performed using logistic regression analysis, and any differences were investigated using the χ^2 test and Student's t test. Differences between groups were evaluated by the χ^2 test or G-test for categorical variables, and the Mann–Whitney U test was used for continuous variables. All analyses were performed using SPSS software (Version 18.0; SPSS, Inc., Chicago, IL), and the significance level was set at $p < 0.05$.

Results

Patient characteristics

Among the 23 patients, one patient who had developed grade 3 oral mucositis in a prior course could not receive the chemotherapy and the ED. Table 1 summarizes the characteristics of the other 22 patients who completed this study protocol. There were 10 male and 12 female, and their average age was 67 years, ranging from 44 to 84 years. The oral mucositis that had developed in the prior course was grade 3 in 2 patients, grade 2 in another 15 patients, and grade 1 in the other 5 patients.

mFOLFOX6 + bevacizumab in 8 patient, FOLFIRI + bevacizumab in 8 patients, FOLFIRI + panitumumab in 1 patient, FOLFIRI in 1 patient, XELOX + bevacizumab in 2 patients, and S-1 + cetuximab in 2 patients were used as the first-line (16 cases) or second-line (6 cases) chemotherapy. Dose reduction in 5-FU was performed in 2 patients experiencing grade 3 oral mucositis in the prior chemotherapy using the mFOLFOX6 + bevacizumab regimen, and in 1 patient experiencing grade 2 oral mucositis in the prior chemotherapy using the FOLFIRI + bevacizumab regimen. Also, dose reduction in S-1 was performed in 1 patient experiencing grade 2 oral mucositis in the prior chemotherapy using the

Table 1 Patient outline

Case number	Prior grade of oral mucositis	Regimen	Regimen duration/q (in weeks)	Treatment phase	Gender	Age	PS	Dose reduction
1	3	FOLFIRI + Bmab	2	First line	Male	68	0	5-FU
2	3	FOLFIRI + Bmab	2	First line	Female	75	2	5-FU
3	2	FOLFOX + Bmab	2	First line	Male	59	0	
4	2	FOLFOX + Bmab	2	First line	Male	73	1	
5	2	FOLFOX + Bmab	2	First line	Female	82	1	5-FU
6	2	FOLFOX + Bmab	2	First line	Female	84	1	
7	2	FOLFOX + Bmab	2	Second line	Female	67	0	
8	2	TS-1 + Cmab	3	Second line	Female	59	1	
9	2	TS-1 + Cmab	3	First line	Male	76	0	S-1
10	2	FOLFOX + Bmab	2	First line	Male	63	0	
11	2	FOLFIRI + Bmab	2	First line	Female	73	1	
12	2	FOLFIRI + Bmab	2	First line	Female	73	1	
13	2	FOLFIRI + Bmab	2	Second line	Female	63	0	
14	2	XELOX + Bmab	3	First line	Male	74	1	Capecitabine
15	2	XELOX + Bmab	3	First line	Female	75	1	
16	2	FOLFIRI + Bmab	2	First line	Male	66	0	
17	2	FOLFIRI + Bmab	2	Second line	Female	76	0	
18	1	FOLFOX + Bmab	2	First line	Female	62	0	
19	1	FOLFIRI + Bmab	2	First line	Male	61	0	
20	1	FOLFOX + Bmab	2	First line	Male	44	0	
21	1	FOLFIRI	2	First line	Male	66	0	
22	1	FOLFIRI + Bmab	2	Second line	Female	59	0	

Table 2 The efficacy on oral mucositis and neutropenia by treatment with the ED

Case number	Oral mucositis (prior treatment)	Oral mucositis (first treatment)	Oral mucositis (second treatment)	Efficacy (first treatment)	Efficacy (second treatment)	Neutropenia (prior treatment)	Neutropenia (first treatment)	Neutropenia (second treatment)	ED intake (first treatment, in g)	ED intake (second treatment, in g)
1	3	1	0	Excellent	Excellent	2	1	0	720	560
2	3	2	1	Good	Excellent	3	1	1	560	480
3	2	0	0	Excellent	Excellent	2	0	0	720	480
4	2	2	1	No change/poor	Good	2	2	1	240	240
5	2	1	0	Good	Excellent	2	1	0	480	560
6	2	1	1	Good	Good	3	2	1	480	400
7	2	1	0	Good	Excellent	0	0	0	800	560
8	2	1	1	Good	Good	0	0	0	560	420
9	2	1	1	Good	Good	0	0	0	480	480
10	2	1	0	Good	Excellent	0	0	0	560	480
11	2	1	0	Good	Excellent	0	0	1	560	560
12	2	0	0	Excellent	Excellent	1	0	0	800	800
13	2	1	1	Good	Good	1	0	0	560	480
14	2	0	0	Excellent	Excellent	0	0	0	720	640
15	2	2	1	No change/poor	Good	0	2	1	1120	1120
16	2	1	0	Good	Excellent	1	2	0	880	800
17	2	1	3	Good	No change/poor	0	0	0	880	960
18	1	0	0	Good	Good	1	0	0	400	560
19	1	0	0	Good	Good	0	0	0	240	240
20	1	1	0	No change/poor	Good	0	0	0	320	320
21	1	1	1	No change/poor	No change/poor	0	0	0	400	640
22	1	0	0	Good	Good	1	0	0	720	480

The efficacy of the ED was categorized as “excellent” in those cases where the maximum grade of oral mucositis was reduced by two grades, as “good” where the maximum grade was reduced by one grade, and as “no change/poor” where there was no reduction in the maximum grade

S-1 + cetuximab regimen, and in capecitabine in 1 patient experiencing grade 2 oral mucositis in the prior chemotherapy using the XELOX + bevacizumab regimen (Table 1).

The average ED intake in the first course was 600 g, ranging from 240 to 1120 g, and was 557 g in the second course, ranging from 240 to 1120 g (Table 2).

Preventive effect on oral mucositis and neutrophil depletion

Table 2 shows the grades of oral mucositis and neutropenia before and after the ED treatment. The maximum grade of oral mucositis decreased in 18 of 22 patients during the first course and in 20 of 22 patients in the second course, compared to those in the prior chemotherapy course. The grade of oral mucositis was significantly reduced by the ED treatment ($p = 0.0002$, prior treatment vs. first treatment; $p < 0.0001$, prior treatment vs. second treatment) (Fig. 1). The efficacy of the ED was categorized as "excellent" in those cases where the maximum grade of oral mucositis was reduced by two grades or more, as "good" where the maximum grade was reduced by one grade, and as "no change/poor" where there was no reduction in the maximum grade. In those 18 patients who received chemotherapy of a 2-week cycle, we investigated the correlation, if any, between the efficacy of the ED (categories) and the ED intake. There was a significant difference in ED intake between the excellent vs. the no change/poor (747 ± 46 vs. 267 ± 46 g, $p < 0.001$) and between the good vs. the no change/poor (607 ± 172 vs. 267 ± 46 g, $p < 0.006$) in ED intake in the first course, and between the excellent vs. the good (600 ± 128 vs. 450 ± 128 g, $p = 0.034$) in ED intake in the second course, and between the excellent vs. the good (1290 ± 244 vs. 923 ± 239 g, $p = 0.009$) in total ED intake in the first plus second courses (Table 3).

The severity of oral mucositis showed a tendency to increase with the severity of neutropenia, in the prior chemotherapy course ($p = 0.083$) (data not shown). The neutropenia was improved particularly by the second treatment with the ED ($p < 0.327$, prior treatment vs. first treatment; $p = 0.038$, prior treatment vs. second treatment) (Fig. 2).

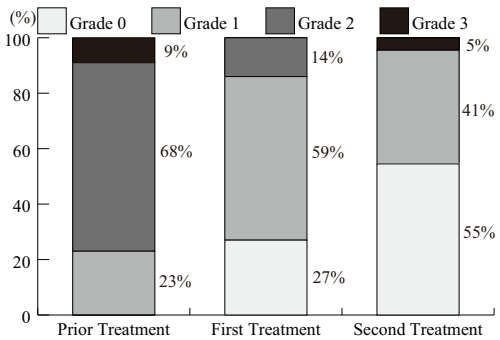

Fig. 1 Preventive effects by the ED on oral mucositis. The oral mucositis was significantly reduced ($p = 0.004$, prior treatment vs. first treatment; $p < 0.001$, prior treatment vs. second treatment) by the ED

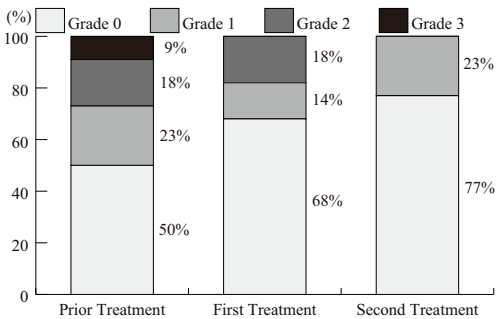

Fig. 2 Preventive effects by the ED on neutropenia. The neutropenia was significantly improved ($p < 0.327$, prior treatment vs. first treatment; $p = 0.038$, prior treatment vs. second treatment) by treatment with the ED

Table 3 The efficacy of ED on oral mucositis and the ED intake

Efficacy	First treatment	Second treatment
Excellent	3 cases/747 ± 46 g	8 cases/600 ± 128 g (1290 g)
Good	12 cases/607 ± 172 g	8 cases/450 ± 128 g (923 g)
No change/poor	3 cases/267 ± 46 g	2 cases/600 ± 509 g (1160 g)

(): total intake of ED (first plus second treatment courses). First treatment: $p = 0.197$ (excellent vs. good), $p < 0.001$ (excellent vs. no change/poor), $p = 0.006$ (good vs. no change/poor). Second treatment: $p = 0.034$ (excellent vs. good), $p = 0.406$ (good vs. no change/poor). First plus second treatments: $p = 0.009$ (excellent vs. good), $p = 0.699$ (excellent vs. no change/poor), $p = 0.481$ (good vs. no change/poor)

Logistic regression analysis for the factors relating to the efficacy by the ED on oral mucositis

Among the 44 courses of ED in the 22 patients, the efficacy was excellent in 14 courses, good in another 24 courses, and no change/poor in the other 6 course (Table 2). The logistic regression analysis revealed that prior administration of ED, the dose reduction in 5-FU or oral fluoropyrimidine, and the ED intake were each an independent significant factor statistically correlated to the preventive efficacy by the ED (the excellent) on the oral mucositis (Table 4).

Discussion

In the present pilot study, the findings indicated that the amino-acid-rich ED Elental® might reduce the incidence and severity of oral mucositis dose-dependently in metastatic colorectal cancer patients receiving fluorouracil-based chemotherapy. However, 5 of the 22 patients (23 %) received dose reductions of 5-FU or oral fluoropyrimidine in chemotherapy in the cycles after Elental® diet. This dose reduction itself would decrease the grade of oral mucositis and could be the

Table 4 Multivariate analysis for the factors related to the efficacy of the ED on oral mucositis

Factor	*p* value	Hazard ratio	95 % CI
Prior administration of ED	0.023	99.423	1.879–5261
Dose reduction of 5-FU/oral fluoropyrimidine	0.034	1019.912	1.674–621,200
ED intake	0.039	1.015	1.001–1.030
Regimen 2 weeks (vs. 3 weeks)	0.051	5.886	0.986–3.418
Male	0.060	230.525	0.800–66,430
Pretreatment albumin value	0.094	75.445	0.482–11,820

reason for the significant difference. Our additional analysis only in those patients who received the same dose of chemotherapy before and after Elental® therapy confirmed the similar efficacy of Elental®. The maximum grade of oral mucositis decreased in 13 of 17 patients during the first course and in 15 of 17 patients in the second course, compared to those in the prior chemotherapy course. The grade of oral mucositis was significantly reduced by the ED treatment ($p < 0.0001$, prior treatment vs. first treatment; $p < 0.0001$, prior treatment vs. second treatment) (data not shown). The logistic regression multivariate analysis revealed that the pretreatment with the ED and the ED intake were important for prevention of oral mucositis by the ED as well as the dose reduction in fluorouracil. The results suggest a possible significance of the nourishment intervention for prevention of chemotherapy-induced oral mucositis.

It is known that cancer produces a state of glutamine deficiency [12], and many nutritional supplements are designed with cancer patients in mind to contain free L-glutamine, which is the preferred substrate for enterocytes within the GI tract. L-Glutamine encourages protein synthesis, enterocyte proliferation, and antiinflammatory effects—each of which plays a role in preventing mucositis [8, 13, 14]. In advanced colorectal cancer patients receiving 5-FU/LV chemotherapy, Choi et al. [15] reported the preventive efficacy of high-dose peroral glutamine (30 g/day) on oral mucositis. However in general, the systemic administration of L-glutamine alone is 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 (MASCC/ISOO) in 2007 [16]. In the present pilot study, we used a small dose of L-glutamine ranging from 5.8 to 27 g during the 14 or 21 days of chemotherapy. Therefore, the efficacy of the ED for preventing oral mucositis is thought to depend on general nutritional intervention involving a well-balanced amino acid mixture including L-glutamine, rather than on L-glutamine alone.

It is reported that the severity of the neutropenia has been associated with the incidence and severity of chemotherapy-induced oral mucositis [17]. Of interest, nourishment intervention using ED in the present study apparently controlled the neutrophil depletion, suggesting the potential of nourishment intervention as an adverse-event measure in cancer chemotherapy. It has been shown that anorexia promotes the generation of other adverse experiences [18], suggesting the importance of the nutritional intervention in cancer chemotherapy. Individual amino acids such as glutamine and arginine which are main constituents of the ED may prevent neutropenia via activation of cellular immunity [19]. However, treatment with glutamine or arginine alone seems to be insufficient for preventing neutropenia [14]. It is expected that the relationship between the nutrient state and the preventive effects of nutritional intervention on neutropenia and the oral mucositis may be clarified by future studies.

Recently, some studies are reported on keratinocyte growth factor (palifermin) [20, 21] and a sustained-release drug of glutamine (Saforis) [22] reducing the incidence of chemotherapy-induced mucositis. The Food and Drug Administration (FDA) of the United States Department of Health and Human Services approved palifermin as prevention and as a treatment for oral mucositis in blood cancer patients who develop marrow toxicity and need hemopoietic stem cell transplantation. However, another consideration is the high cost of these new drugs [23] for introduction into clinical practice. Therefore, nourishment intervention using ED for oral mucositis should be considered alongside other standard oral care for sustaining the patient's QOL.

We conclude that the amino-acid-rich elemental diet Elental® may be useful as a countermeasure for 5-FU-based chemotherapy-induced oral mucositis in patients with colorectal cancer in association with controlling neutropenia. The findings from this prospective pilot study warrant the initiation of a new clinical study with nutritional intervention in colorectal cancer patients developing oral mucositis. However, this small study makes any conclusions limited. We have conducted a multicenter clinical study clarifying the preventive effects on oral mucositis by Elental® and its correlation with change of amino acid balance in the serum.

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Authors' contributions YO was the principal investigator and study coordinator. YO developed the protocol. NI, KY, SU, HK, GN, MT, YA, and YO collected, analyzed, and helped to interpret the data.

Conflict of interest The authors declare that they have no competing interests.

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