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Randomized control trials

Randomized study of the effect of synbiotics during neoadjuvant chemotherapy on adverse events in esophageal cancer patients☆

Masaaki Motoori [a, *], Masahiko Yano [a], Hiroshi Miyata [a], Keijiro Sugimura [a], Takuro Saito [a], Takeshi Omori [a], Yoshiyuki Fujiwara [a], Norikatsu Miyoshi [a], Hirofumi Akita [a], Kunihito Gotoh [a], Hidenori Takahashi [a], Shogo Kobayashi [a], Shingo Noura [a], Masayuki Ohue [a], Takashi Asahara [b], Koji Nomoto [b], Osamu Ishikawa [a], Masato Sakon [a]

[a] Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka, 537-8511, Japan
[b] Yakult Central Institute, 1796 Yaho, Kunitachi, Tokyo, 186-8650, Japan

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SUMMARY

Background and aims: The clinical value of synbiotics in patients receiving neoadjuvant chemotherapy currently remains unclear. The aim of this study was to investigate the effects of synbiotics in esophageal cancer patients receiving neoadjuvant chemotherapy on the intestinal microbiota and the adverse events of chemotherapy.

Methods: Sixty-one patients with advanced esophageal cancer who were scheduled to receive neoadjuvant chemotherapy were randomly allocated to 2 groups. One group received synbiotics during chemotherapy (n = 30), while the other group did not (n = 31). The fecal microbiota and organic acid concentrations were analyzed. The primary endpoint was the incidence of chemotherapy-related adverse events.

Results: The numbers of beneficial and harmful bacteria were significantly larger and smaller, respectively, in the synbiotics group than in the control group on day 10 of chemotherapy. The concentrations of acetic acid and propionic acid were significantly higher in the synbiotics group on day 10 of chemotherapy. The frequencies of severe lymphopenia and diarrhea were significantly less in the synbiotics group than in the control group (P = 0.033, 0.035, respectively). Furthermore, febrile neutropenia occurred less in the synbiotics group (10/30 in the synbiotics group vs 19/31 in the control group, P = 0.029).

Conclusions: Synbiotics during neoadjuvant chemotherapy in esophageal cancer patients reduced the occurrence of adverse events of chemotherapy through adjustments to the intestinal microbiota. (University Hospital Medical Information Network (http://www.umin.ac.jp), registration number UMIN000006875).

1. Introduction

Neoadjuvant chemotherapy followed by surgery represents a promising treatment strategy for improving the prognosis of patients with advanced esophageal cancer [1]. Chemotherapy is performed to obtain antitumor effects, but causes various toxicities, such as myelosuppression, diarrhea, and febrile neutropenia. These adverse events sometimes lead to the interruption of chemotherapy or reductions in the dosage of drugs administered. The effect of chemotherapy is considered to be dose-dependent, while the dose administered is limited by adverse events. To obtain a higher response rate, more active chemotherapy regimens involving triplet chemotherapy have been more frequently used in recent years [2,3]. These powerful regimens have been associated with a higher incidence of severe toxicities. Moreover, patients with advanced esophageal cancer are generally aged and malnourished due to malignant esophageal stenosis. Therefore, it is important to develop a method to reduce chemotherapy-related toxicities.

The intestinal tract is the largest immune organ in the human body and is considered an important target organ of severe insults.

☆ The study protocol was registered in the University Hospital Medical Information Network (http://www.umin.ac.jp; registration number ID 000006875).

* Corresponding author. Tel.: +81 6 6972 1181; fax: +81 6 6981 8055.
E-mail address: mmotoori@gh.opho.jp (M. Motoori).

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Chemotherapy is a major aggressor that may injure the intestinal mucosa and disturb the intestinal microbiota [4]. Disturbances to the microbiota may reduce production of organic acids in the bowel and lead to the loss of mucosal integrity, impaired clarification of harmful bacterium, and decreased anti-inflammatory reactions. These phenomena may induce various chemotherapy-related toxicities such as diarrhea and infectious complications.

Probiotics are viable bacteria that can improve the intestinal microbiota [5]. Prebiotics are non-digestible food constituents that selectively alter the growth of certain host beneficial bacteria [6]. The combination of probiotics and prebiotics is called synbiotics. Synbiotics were previously shown to be beneficial for patients with biliary cancer undergoing hepatobiliary resection [7], those with esophageal cancer undergoing esophagectomy [8], or those with severe systematic inflammatory response syndrome [9]. However, few studies have investigated the significance of synbiotics in patients receiving chemotherapy.

The purpose of the present study was to elucidate the impact of the administration of synbiotics during neoadjuvant chemotherapy in advanced esophageal cancer patients on the fecal microbiota and chemotherapy-related adverse events.

2. Materials and methods

2.1. Patients

The eligibility criteria of this study were as follows; 1) histopathologically confirmed and previously untreated thoracic esophageal cancer; 2) clinical stage IB, II, III, or IV without distant organ metastasis; 3) scheduled to undergo neoadjuvant chemotherapy; 4) age >20 and < 80 years; 5) an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; 6) adequate organ function (leukocyte count > 3500/mm^3, platelet count > 100,000/mm^3, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels no greater than 2.5 times the upper limit of the normal range; total bilirubin level of no greater than 1.8 mg/dl; and serum creatinine <1.3 mg/dl); 7) dysphagia score of 2 or less. Exclusion criteria were as follows; 1) uncontrolled diabetes; 2) esophago-tracheal or esophago-mediastinal fistula. Patients were staged according to the criteria of the International Union Against Cancer (UICC) [10].

2.2. Study design and treatment

This study is an open-labeled randomized prospective clinical trial in a single center. Patients were randomly allocated to either the synbiotics group or control group before chemotherapy in a 1:1 ratio. Stratification factors were gender and serum albumin levels. Randomization was performed by permuted block method with block sizes of 4. Data center in the Department of Surgery Osaka Medical Center for Cancer and Cardiovascular Diseases generated a randomization table.

The regimen of neoadjuvant chemotherapy consisted of docetaxel, cisplatin, and 5-fluorouracil (5-FU) (DCF therapy). Docetaxel was administered at 70 mg/m^2, cisplatin at 70 mg/m^2 by drip infusion on day 1; and 5-FU at 700 mg/m^2 administered by continuous infusion on day 1 through day 5 [11]. Two courses of chemotherapy were provided, separated by a 3-week interval. When the tumor did not shrink after the first course of chemotherapy or severe adverse events occurred during the first course of chemotherapy, neoadjuvant chemotherapy was stopped at the first course. Supportive therapy and prophylaxis against expected adverse events, such as antiemetics and dexamethasone, were provided. No prophylactic antibiotics or granulocyte colony-stimulating factor (G-CSF) were provided. Antibiotics were used for febrile neutropenia or suspicious infections. G-CSF was used when febrile neutropenia was occurred. Patients underwent surgery 4–6 weeks after the last day of chemotherapy if curative resection was considered possible. When curative resection was considered impossible, patients underwent chemoradiotherapy or palliative chemotherapy.

During the overall period of neoadjuvant chemotherapy, patients took oral diet, basically. If a patient could not take enough diet due to esophageal stenosis, the patient drank enteral nutrients. When oral intake decreased due to adverse events of chemotherapy, parenteral nutrition support was performed. Patients allocated to the synbiotics group were administered Yakult BL Seichoyaku (3g/day, Yakult Honsha, Tokyo), containing 1×10^8 living *Bifidobacterium breve* strain Yakult (*B. breve* strain Yakult) and 1×10^8 living *Lactobacillus casei* strain Shirota (*L. casei* strain Shirota)/g, and galacto-oligosaccharides (15 g/day, Oligomate S-HP; Yakult Honsha). Patients allocated to the control group were administered Biofermin (3 g/day, Takeda, Osaka, Japan), containing 1 x 10^9 *Streptococcus faecalis* (*S. faecalis*). Synbiotics or Biofermin treatment started two days before the start of chemotherapy and continued during the entire course of chemotherapy (for 6 weeks).

2.3. Fecal bacteriologic analysis

Fecal samples were collected before administration of synbiotics or Biofermin, one day before the initiation of chemotherapy, day 10 of the first cycle of chemotherapy, and one day before the initiation of the second cycle of chemotherapy. To quantify the bacteria present in the samples, we extracted total RNA fractions from feces and examined the gut microbiota composition using 16 S or 23 S ribosomal RNA (rRNA)-targeted reverse transcription-quantitative PCR (RT-qPCR) using the Yakult Intestinal Flora-SCAN as described previously [12,13]. The concentrations of organic acids and fecal pH were measured as described previously. [14].

2.4. Serum diamine oxidase activity

Blood samples were collected before administration of synbiotics or Biofermin, day 10 of the first cycle of chemotherapy, and one day before the initiation of the second cycle of chemotherapy. Sera were obtained from blood samples and stored at −80 °C until use. Serum diamine oxidase (DAO) activity, which is one of the markers of intestinal integrity, was measured by an immunoassay using an ELISA kit (Immundiagnostik, Bensheim, Germany) according to the manufacturer's protocol.

2.5. Evaluation of response to chemotherapy

Patients underwent CT scans before and 10 days after the completion of chemotherapy. The largest area of the primary esophageal cancer was measured in two dimensions, using the greatest diameter and the greatest perpendicular distance. Patients with $\geq$ 50% decrease were defined as responders.

2.6. Evaluation of chemotherapy-related toxicities

Chemotherapy-related toxicities were evaluated using the toxicity grading criteria of National Cancer Institute Common Terminology Criteria for Adverse Events version 4 during the first cycle. Dose reductions in the second cycle were based on toxicities in the first cycle: (1) grade 4 leukopenia or neutropenia persisting for > 5 days; (2) grade 4 thrombocytopenia; (3) grade 3 or higher non-hematological toxicities, except for anorexia, vomiting, nausea, constipation, fatigue, stomatitis, electrolyte abnormalities, and diarrhea that resolved after 3 days.

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