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Phase II multi-institutional prospective randomised trial comparing S-1 + paclitaxel with S-1 + cisplatin in patients with unresectable and/or recurrent advanced gastric cancer

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BACKGROUND: A combination of S-1 and cisplatin has been shown to be effective with acceptable safety for the first-line treatment of far-advanced gastric cancer in Japan. This is the first randomised phase II trial to compare S-1 + paclitaxel with S-1 + cisplatin in this setting.

METHODS: Patients with unresectable and/or recurrent advanced gastric cancer were randomly assigned to receive one of the two regimens: S-1 (40 mg m^{-2} twice daily) on days 1–14 plus paclitaxel (60 mg m^{-2}) on days 1, 8, and 15 of a 4-week cycle (S-1 + paclitaxel) or S-1 (40 mg m^{-2} twice daily) on days 1–21 plus cisplatin (60 mg m^{-2}) on day 8 of a 5-week cycle (S-1 + cisplatin). The primary end point was the response rate (RR). Secondary end points included progression-free survival (PFS), overall survival (OS), and safety.

RESULTS: A total of 83 patients were eligible for safety and efficacy analyses. In the S-1 + paclitaxel and S-1 + cisplatin groups, RRs (52.3% *vs* 48.7%; $P=0.74$) and median PFS (9 *vs* 6 months; $P=0.50$) were similar. The median OS was similar in the S-1 + paclitaxel and S-1 + cisplatin groups (16 *vs* 17 months; $P=0.84$). The incidence of grade 3 or higher haematological toxicity was 19.0% with S-1 + paclitaxel and 19.5% with S-1 + cisplatin. The incidence of grade 3 or higher non-haematological toxicity was 14.2% with S-1 + paclitaxel and 17.1% with S-1 + cisplatin.

CONCLUSION: S-1 + paclitaxel was suggested to be a feasible and effective non-platinum-based regimen for chemotherapy in patients with advanced gastric cancer. Our results should be confirmed in multicenter, phase III-controlled clinical trials.

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Gastric cancer is the second most common cause of cancer-related mortality worldwide. Patients with unresectable or recurrent gastric cancer have extremely poor outcomes, with 5-year survival rates of <5%. Various chemotherapeutic agents have been used in the hope of improving overall survival (OS), progression-free survival (PFS), response rate (RR), and quality of life in patients with advanced gastric cancer.

The SPIRITS trial established that S-1 + cisplatin is a standard first-line regimen for advanced gastric cancer in Japan (Koizumi *et al*, 2003; Koizumi *et al*, 2008). This randomised phase III study compared OS between patients who were given S-1 + cisplatin and those who were given S-1 alone (Koizumi *et al*, 2008). Median OS was significantly longer in the S-1 + cisplatin group than in the S-1 alone group. On the other hand, the S-1 + cisplatin group had more toxic events, such as neutropenia, anaemia, nausea, and anorexia; however, there was no treatment-related mortality. Subsequently, the JCOG 9912 study confirmed that oral S-1 could replace infusional 5-fluorouracil without compromising efficacy or causing excessive toxicity (Boku *et al*, 2009). Based on these findings, S-1 + cisplatin has been recognised as a standard chemotherapy regimen for advanced gastric cancer in Japan. However, no alternative standard regimen is currently available for this indication. Some patients with impaired renal function cannot receive S-1 + cisplatin as a first-line treatment for advanced gastric cancer. Therefore, other regimens with low toxicity are needed.

Paclitaxel is a taxane derivative that was originally isolated from *Taxus brevifolia*, a type of Western yew (Wani *et al*, 1971). Paclitaxel has activity against a broad range of tumour types, including breast, ovarian, and lung cancers (Holmes *et al*, 1991; Einzig *et al*, 1992; Chang *et al*, 1993). Paclitaxel is also an effective drug for gastric cancer, with RRs ranging 20–28% in single-agent phase II studies (Ajani *et al*, 1998; Ohtsu *et al*, 1998; Yamada *et al*, 2001; Yamaguchi *et al*, 2002). The recommended dosage of paclitaxel in Japan was determined to be 210 mg m^{-2} once every 3 weeks (Yamaguchi *et al*, 2002). Recently, good results have been

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obtained with a weekly regimen of paclitaxel in patients with ovarian cancer and gastric cancer (Fennelly *et al*, 1997; Hironaka *et al*, 2006). To further improve outcomes, many phase II studies have been performed to evaluate the safety profile and efficacy of weekly paclitaxel-based combination regimens for advanced and metastatic gastric cancer (Sakamoto *et al*, 2009). In 2006, we performed a phase I/II study of weekly paclitaxel combined with S-1 in patients with unresectable and/or recurrent advanced gastric cancer (Mochiki *et al*, 2006). The RR was 54.1%, and the median survival time was 15.5 months. Our results showed that S-1 + paclitaxel is effective and well tolerated (Mochiki *et al*, 2006). To confirm our findings, we planned the present randomised phase II study to compare the efficacy and safety of S-1 + paclitaxel with those of S-1 + cisplatin, currently the standard treatment in Japan, in patients with advanced gastric cancer.

PATIENTS AND METHODS

Patients

Patients between 20 and 75 years of age who had advanced, unresectable, histologically confirmed adenocarcinoma of the stomach were eligible for enrolment in this study. Eligible patients also had to have measurable or evaluable lesions, the ability to orally intake medications, an Eastern Clinical Oncology Group performance status of 0 or 1, and adequate liver, kidney, and bone marrow functions, similar to our previous study (Mochiki *et al*, 2006). Patients were excluded if they had brain metastases, significant gastrointestinal bleeding, serious comorbidity, concomitant use of drugs that potentially interact with S-1 (flucytosine, allopurinol, warfarin, or phenytoin), or an inability to comply with the protocol requirements. Pregnant women were also excluded.

Study design and randomisation

This randomised, open-label, phase II study was conducted at six institutions in Gunma and Saitama Prefectures in Japan between January 2006 and November 2010. The protocol was approved by the ethics committee of each participating institution, and all patients gave written informed consent. The primary end point of the study was the clinical response (RR) to the study treatment (S-1 + paclitaxel) as compared with the response to the control treatment (S-1 + cisplatin) in patients with advanced gastric cancer. Secondary end points were median OS, PFS, and safety. These variables were compared between the treatment groups.

A central data centre confirmed patient eligibility, and eligible patients were randomly assigned to treatment automatically according to stratification factors (prior therapy and performance status). Randomisation was centrally performed by the Coordination Centre of Gunma University.

Treatment regimens

Patients who were assigned to the S-1 + paclitaxel group received S-1 orally (40 mg m^{-2} twice daily) on days 1–14 plus paclitaxel (60 mg m^{-2}) as an intravenous infusion on days 1, 8, and 15 of a 4-week cycle (Mochiki *et al*, 2006). Patients who were assigned to the S-1 + cisplatin group received S-1 orally (40 mg m^{-2} twice daily) on days 1–21 plus cisplatin (60 mg m^{-2}) as an intravenous infusion on day 8 of a 5-week cycle (Koizumi *et al*, 2003).

Before treatment with paclitaxel in the S-1 + paclitaxel group, patients received an antihistamine (e.g., diphenhydramine hydrochloride 50 mg), dexamethasone 8 mg, and cimetidine 300 mg (or a comparable H2 blocker) to prevent paclitaxel-related hypersensitivity reactions. To reduce the risk of cisplatin-induced renal damage in the S-1 + cisplatin group, patients received hydration with 1500 ml of 5% glucose before treatment with cisplatin. Furosemide was given 30 min before starting the cisplatin infusion, and hydration with 4000 ml of 5% glucose, 24 g NaCl, 1.2 g KCl and 0.8 g $CaCl_2$ was continued for 48 h. Treatment was discontinued at the onset of disease progression, severe toxic effects, or at the patient's request.

Response and toxicity criteria

Tumour response was assessed objectively after each course of treatment, according to the Response Evaluation Criteria in Solid Tumours. OS was estimated from the date of study entry to the date of death or the last follow-up visit according to the Kaplan–Meier method. The log-rank test was used to compare survival between treatment groups. Progression free survival was measured from the date of study entry to the first objective observation of disease progression or death from any cause. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0.

Follow-up schedule

Disease progression and the development of new lesions were evaluated as needed by abdominal radiography, abdominal and thoracic computed tomography, and measurement of the tumour markers carcinoembryonic antigen (CEA) and CA 19–9, performed at baseline and at least every 4–5 weeks during treatment. Responses were evaluated every 8 weeks or earlier in patients who had an evidence of treatment failure. Physical examinations, complete blood counts, serum chemical analyses, and other laboratory tests were performed before treatment and at least every 2 weeks during treatment.

Statistical analysis

The required sample size was estimated according to the criteria of Simon *et al* (1985). We estimated that 36 patients per treatment group would allow selection of the better treatment with 90% accuracy, given that the absolute difference in the RR of the better treatment is at least 15%, with an expected baseline RR of 50%. To compensate for the possible enrolment of ineligible patients, the sample size was set at 80 (40 patients per group).

The Kaplan–Meier estimates and a Cox proportional hazards model were used to analyse time-event variables. The distributions of discrete variables were compared between the two treatment groups with the use of the χ^2-test or Fisher's exact test as appropriate. To compare continuous variables, the Mann–Whitney *U*-test for nonparametric data was used. All the tests were two-sided, and *P* values <0.05 were considered to indicate statistical significance. SPSS software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

RESULTS

Patient characteristics

Between January 2006 and November 2010, a total of 83 patients (61 men and 22 women) were registered at six hospitals. In all, 42 patients were assigned to S-1 + paclitaxel and 41 patients were assigned to S-1 + cisplatin. The characteristics of the assessable patients, including sex, median age, performance status, histological type, prior therapy, and sites of metastasis, are shown in Table 1. The mean age of the patients was 63.3 years in the S-1 + paclitaxel group and 63.0 years in the S-1 + cisplatin group. The baseline characteristics were well balanced between the two treatment groups.

Response rate

The confirmed RR was 52.3% (22 out of 42) in the S-1 + paclitaxel group (95% confidence interval (CI), 39–61%) and 48.7% (20 out

Table 1 Characteristics of patients

	S-1 + paclitaxel	S-1 + cisplatin	*P*-value
Sex: male/female	31/11	30/11	0.48
Mean age ± s.e.; years	63.3 ± 1.4	63.0 ± 1.3	0.91
Performance status 0/1	38/4	39/2	0.42
Histological type			
Intestinal	16	16	0.47
Diffuse	26	25	
Prior therapy			
None	33	33	0.73
Gastrectomy	2	3	
Gastrectomy + chemotherapy	7	5	
Site of metastasis			
Liver	14	12	0.57
Lymph nodes	40	33	
Peritoneum	11	8	

Table 2 Overall response to treatment

	S-1 + paclitaxel	S-1 + cisplatin	*P*-value
CR	1	0	0.72
PR	21	20	
SD	12	10	
PD	6	8	
NE	2	3	

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SR = stable disease.

of 41) in the S-1 + cisplatin group (95% CI, 39–61%) (Table 2). All the responses were partial, except for one complete response (CR) in the S-1 + paclitaxel group. The RR in the S-1 + paclitaxel group was slightly, but not significantly, higher than that in the S-1 + cisplatin group ($P = 0.74$). The tumour control rate (CR + partial response + stable disease) was 80% (34 out of 42) in the S-1 + paclitaxel group and 73% (30 of 41) in the S-1 + cisplatin group.

Progression-free survival and overall survival

The median PFS was 9 months in the S-1 + paclitaxel group (95% CI, 6–12 months) and 6 months in the S-1 + cisplatin group (95% CI, 4–9 months; Figure 1). The hazard ratio for disease progression or death (S-1 + paclitaxel/S-1 + cisplatin) was 0.84 (95% CI, 0.50–1.4). When the treatment groups were compared by log-rank test, there was no significant difference in median PFS ($P = 0.50$). At a median follow-up of 14 months, the median OS was 16 months in the S-1 + paclitaxel group (95% CI, 15–22 months) and 17 months in the S-1 + cisplatin group (95% CI, 11–23 months); the hazard ratio for death (S-1 + paclitaxel/S-1 + cisplatin) was 0.94 (95% CI, 0.55–1.63). Efficacy of the treatments thus appeared to be similar (log-rank test; $P = 0.84$; Figure 2). The estimated survival rates at 1 and 2 years were 70% and 26%, respectively, in the S-1 + paclitaxel group and 63% and 30%, respectively, in the S-1 + cisplatin group.

A total of 14 patients (S-1 + paclitaxel, 6 patients; S-1 + cisplatin, 8 patients) underwent gastrectomy after chemotherapy and had no critical chemotherapy-related adverse effects. On average, the number of administered courses of chemotherapy before surgery was 5.1 (range 2–15) in the S-1 + paclitaxel group and 4.1 (range 2–8) in the S-1 + cisplatin group. Total gastrectomy was performed in 13 patients and distal gastrectomy was done in 1. The six patients in the S-1 + paclitaxel group had a median survival of 28

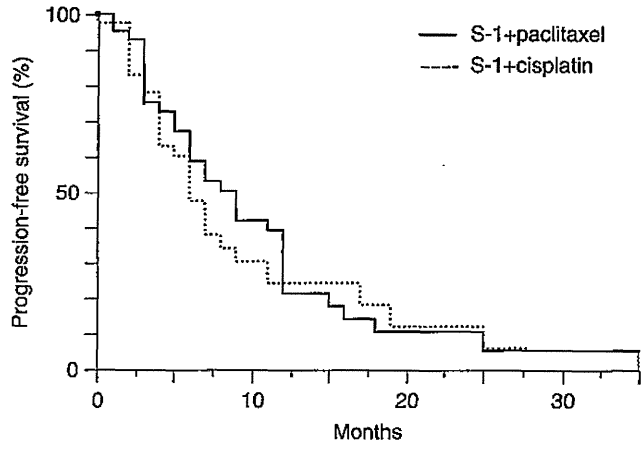

Figure 1 Progression free survival.

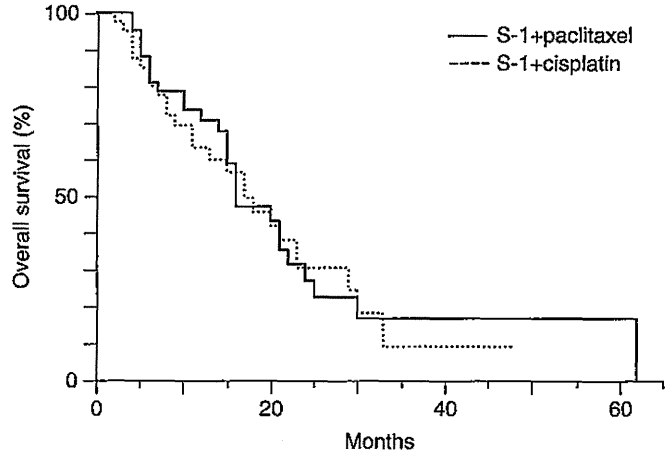

Figure 2 Overall survival.

months (range 21–60), and two patients were alive at the time of this analysis. The eight patients in arm C had a median survival of 25.5 months (range 11–48), and all were alive at the time of this analysis. Responses of all the patients who underwent gastrectomy were partial.

Toxic effects

The median number of administered cycles of chemotherapy was 5 (range 2–30) in the S-1 + paclitaxel group and 4 (range 1–15) in the S-1 + cisplatin group. Myelosuppression was the most frequent toxic effect in both groups (Table 3). In the S-1 + paclitaxel group, grade 3 or 4 haematological toxicity occurred in 19.0% (8 out of 42) of the patients and grade 3 or 4 non-haematological toxicity occurred in 14.2% (6 out of 42) of the patients. The most common types of severe (grade 3 or 4) haematological toxicity were leucopenia (3 patients, 7.1%), neutropenia (3 patients, 7.1%), and anaemia (2 patients, 4.7%) (Table 3). The most common types of all grade non-haematological toxicity were peripheral neuropathy (7 patients, 16.6%), anorexia (6 patients, 14.2%), diarrhoea (5 patients, 11.9%), nausea (5 patients, 11.9%), and stomatitis (5 patients, 11.9%). In the S-1 + cisplatin group, grade 3 or 4 haematological toxicity occurred in 19.5% (8 out of 41) of the patients and grade 3 or 4 non-haematological toxicity occurred in 17.1% (7 out of 41). The frequent types of severe (grade 3 or 4) haematological toxicity were neutropenia (4 patients, 9.7%), leucopenia (3 patients, 7.5%), and anaemia (2 patients, 5%) (Table 3). There was one episode of febrile neutropenia. The most

Table 3 Toxic effects and number of patients with toxicity

	S-1 + paclitaxel		S-1 + cisplatin	
Grade	**1-2**	**3-4**	**1-2**	**3-4**
Haematological toxicity				
Leucopenia	10	3	11	2
Neutropenia	10	3	6	4
Anaemia	3	2	8	2
Thrombocytopenia	1	0	8	0
Non-haematological toxicity				
Anorexia	6	0	12	2
Nausea	5	0	10	2
Diarrhoea	3	2	9	1
Fatigue	3	0	6	0
Stomatitis	4	1	3	0
Peripheral neuropathy	4	3	2	0
Hypoalbuminemia	2	0	6	0
Bilirubin	1	0	1	0
AST/ALT	2	0	0	1
Hyperkalemia	3	0	0	0
Hyponatremia	0	0	0	1

Abbreviations: ALT = alanine aminotransferase; AST = aminotransferase.

common types of all grade non-haematological toxicity were anorexia (14 patients, 34.1%), diarrhoea (10 patients, 24.3%), and nausea (12 patients, 29.2%). Treatment was discontinued during the first course of S-1 + cisplatin in three patients because of grade 3 liver dysfunction, grade 3 anorexia, and grade 4 neutropenia, respectively. There was no treatment-related death or severe delayed toxicity in either group. The overall incidence of grade 3 or 4 toxic effects did not differ significantly between the treatment groups ($P = 0.53$).

DISCUSSION

The efficacy of S-1-based combination chemotherapy in advanced gastric cancer has been assessed in a number of phase I/II studies. The SPIRITS trial, a phase III study, established S-1 + cisplatin as a standard first-line regimen for advanced gastric cancer in Japan (Koizumi *et al*, 2008). However, the FLAGS trial, a non-Asian global phase III study, concluded that S-1 + cisplatin did not prolong the OS of patients with advanced gastric or gastroesophageal adenocarcinoma as compared with cisplatin + infusional fluorouracil, but did have a significantly better safety profile (Ajani *et al*, 2010). Cisplatin can cause renal toxicity, emesis, and peripheral neuropathy, and the intravenous hydration required during its use lengthens outpatient visits and can necessitate overnight admission. Consequently, drug combinations, such as S-1 + cisplatin, are considered too toxic for elderly patients or patients with a poor performance status. S-1 + cisplatin regimens also have other limitations. Therefore, alternative drug combinations with similar efficacy but lower toxicity than S-1 + cisplatin are needed. Our previous phase I/II study showed that a combination of S-1 + paclitaxel is highly effective in advanced and recurrent gastric cancer, with an acceptable and manageable toxicity profile (Mochiki *et al*, 2006). This combination regimen produced promising results, with an overall RR of 54.1%, a median time to progression of 9.5 months (95% CI, 5–11.6 months), and a median OS of 15.5 months) (95% CI, 11.6–19.4 months). Haematological and non-haematological toxicities associated with S-1 + paclitaxel were generally mild. Based on the positive results of our previous study, we initiated the present randomised phase II trial to compare S-1 + paclitaxel with S-1 + cisplatin in a similar setting.

To our knowledge, this is the first randomised trial to compare S-1 + paclitaxel with S-1 + cisplatin in patients with unresectable and recurrent gastric cancer. Although this was a phase II study and had limited power to detect significant differences between the treatment groups, we could estimate the relative efficacy and safety of the two regimens. To assess the primary end point (RR), all images were reviewed and all responses were confirmed. The RR was 52.3% in the S-1 + paclitaxel group and 48.7% in the S-1 + cisplatin group, suggesting that both regimens have similar activity in patients with unresectable and recurrent gastric cancer. The RRs for S-1 + paclitaxel and S-1 + cisplatin are largely consistent with the results of previous studies in advanced gastric cancer (Koizumi *et al*, 2003; Mochiki *et al*, 2006). Furthermore, median PFS and OS were also similar for both regimens in this study. The promising median survival time obtained in the present study (16 months) raises hope that S-1 + paclitaxel may improve survival outcomes in patients with advanced gastric cancer. The longer median OS in our study may have been related to the good performance status of many patients. Performance status was 0 or 1 in all patients; no patient had a performance status of 2. Survival outcomes in our study are consistent with the results of phase II studies of similar regimens of S-1 + paclitaxel in patients with advanced gastric cancer (Narahara *et al*, 2008; Lee *et al*, 2009; Ueda *et al*, 2010). Lee *et al* (2009) obtained an RR of 40% and a median survival time of 12.1 months with a combination regimen of weekly paclitaxel and S-1 in advanced gastric cancer. Nakajo *et al* (2008) reported a median OS of > 17.0 months in their feasibility study of paclitaxel and S-1 in 52 patients with advanced gastric cancer treated at a single institution. In the present study, combination therapy with S-1 and weekly paclitaxel was associated with very tolerable levels of gastrointestinal toxicity as well as high antitumour effectiveness. Furthermore, the survival outcomes with S-1 + paclitaxel were similar to those reported for S-1 + docetaxel, another S-1 taxane-based regimen (Yoshida *et al*, 2006). It is not necessarily surprising that taxanes + S-1 markedly improved outcomes in patients with advanced and metastatic gastric cancer because patients eligible to receive a combination of paclitaxel and oral agents must have the possibility of oral intake, suggesting that they are in better general condition.

Human epidermal growth factor receptor 2 (HER2) is an important biomarker and a key driver of tumourigenesis in gastric cancer, with studies showing overexpression in 7–34% of tumours (Tanner *et al*, 2005; Gravalos and Jimeno, 2008). The ToGA study recently showed that the addition of trastuzumab to chemotherapy improves survival in patients with advanced gastric or gastro-oesophageal junction cancer as compared with chemotherapy alone (Bang *et al*, 2010). The ToGA study also found that OS was longer in patients with high expression of HER2 protein than in those with low expression. Information on the HER2 status of the patients in our study is unfortunately unavailable. However, recent studies have also shown an association of HER-2-positive tumours with poor outcomes and aggressive disease (Tanner *et al*, 2005; Gravalos and Jimeno, 2008). Further studies are thus needed to address the issue of whether HER2 has an effect on outcomes in gastric cancer and to determine whether it confers a good or poor prognosis.

Studies of patients with gastric cancer who receive chemotherapy before gastrectomy may show a survival benefit with the use of perioperative chemotherapy as compared with chemotherapy alone. Neoadjuvant (preoperative) chemotherapy is attractive for a number of reasons, including good compliance of patients with preoperative treatment, higher surgical cure rates as a result of tumour downstaging, and sparing patients with biologically aggressive disease from induction chemotherapy. The MAGIC trial showed that neoadjuvant chemotherapy resulted in tumour downstaging, significantly improved OS from 23–36%, and did not increase the rate of postoperative complications (Cunningham *et al*, 2006). However, favourable outcomes have been obtained

after gastrectomy with R0 resection in patients with resectable as well as those with unresectable disease (Satoh *et al*, 2006). These results stress the importance of precise preoperative staging to identify patients most likely to benefit from neoadjuvant chemotherapy and of using a feasible and highly effective chemotherapeutic regimen.

Overall, treatment compliance and safety were good in both treatment arms, and there were no treatment-related deaths in our study. Both agents were associated with minimal myelosuppression, and the most common haematological toxic effects were leucopenia and neutropenia. In general, S-1 + paclitaxel had a better safety profile and was better tolerated than S-1 + cisplatin. S-1 + cisplatin was characterised by a higher incidence of grade 1 or 2 haematological toxicity, especially anaemia and thrombocytopenia, as compared with S-1 + paclitaxel. One episode of febrile neutropenia occurred in one patient treated with S-1 + cisplatin. Non-haematological toxicity profiles differed between S-1 + paclitaxel and S-1 + cisplatin. The major difference was the higher incidences of anorexia and nausea among the patients treated with S-1 + cisplatin. In contrast, the S-1 + paclitaxel regimen had tolerable gastrointestinal toxicities as well as high antitumour effectiveness. Less than 15% of our patients had grade 3 or higher gastrointestinal toxicities, including anorexia, nausea, and diarrhoea. As compared with S-1 + cisplatin, however, S-1 + paclitaxel has been shown to be more often associated with peripheral neuropathy. Peripheral neuropathy, which usually begins to develop after four cycles of treatment, may have clinical implications; it causes numbness and paraesthesia in a glove- and stocking-like distribution. Severe neurotoxicity precludes long-term treatment with paclitaxel (Sakamoto *et al*, 2009). Therefore, early detection and symptomatic relief are essential clinically. Both haematological and non-haematological toxicities of S-1 + paclitaxel were generally manageable, and most patients could continue treatment in an outpatient setting. With cisplatin-based regimens, patients must receive intravenous infusions to ensure adequate hydration and prevent cisplatin-induced renal damage. S-1 + paclitaxel might therefore be better suited for treatment on an outpatient basis than cisplatin-based chemotherapy. A high RR coupled with a better quality of life is considered an advantage of S-1 + paclitaxel.

S-1 is approved in Japan, China, Taiwan, Korea, and Singapore for the treatment of gastric cancer and more recently has been approved in 27 European countries for the management of advanced gastric cancer (Blum *et al*, 2011). In initial clinical trials of S-1 in the United States and Europe, diarrhoea occurred as dose-limiting toxicity. In early Japanese clinical trials, however, myelosuppression developed as dose-limiting toxicity (Lenz *et al*, 2007). Differences in dose tolerance between Asians and other populations are probably caused by polymorphisms in the CYP2A6 gene (Blum *et al*, 2011). Lower dose intensity may thus explain why S-1 is not always as effective in Western countries as it has been in Japan. There are also marked geographic differences in the prevalences of gastric cancer subtypes. Intestinal-type distal gastric cancer related to *Helicobacter pylori* is predominant in Asia, whereas proximal and diffuse subtypes of gastric cancer are most common in Europe and North America. There are also marked regional differences in how gastric cancer is treated. In Europe, triplet therapy with epirubicin, cisplatin, and fluorouracil (ECF) is widely used on the basis of the results of two randomised studies (Webb *et al*, 1997; Ross *et al*, 2002). The REAL-2 trial is the largest randomised controlled study to date to compare first-line chemotherapy regimens for advanced oesophago-gastric cancer in the United Kingdom (Cunningham *et al*, 2008). The results showed that triplet therapy with epirubicin, oxaliplatin, and capecitabine is at least as efficacious as ECF, with the additional advantages of a more convenient mode of administration (no requirement for hydration) and an acceptable toxicity profile. Because of these appreciable differences between Japan and Western countries, our results may be applicable only to Asian patients with gastric cancer and cannot be directly extrapolated to a Western population.

CONCLUSION

In conclusion, this is the first randomised trial to compare the efficacy and safety of S-1 + paclitaxel with those of S-1 + cisplatin in patients with far-advanced gastric cancer. As a randomised phase II study, our protocol had limited power to directly compare efficacy between the treatment groups. However, our results suggest that both the regimens are active and well-tolerated treatments for unresectable and/or recurrent advanced gastric cancer and indicate that S-1 + paclitaxel merits further evaluation as a reference arm in a subsequent phase III trial.

Conflict of Interest

The authors declare no conflict of interest.

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Original Paper

Central Venous Port System-Related Complications in Outpatient Chemotherapy for Colorectal Cancer

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ABSTRACT

Background/Aims: The current standard chemotherapy for metastatic colorectal cancer is the FOLFOX or the FOLFIRI regimen. Although these regimens include the continuous infusion of an anticancer agent, chemotherapy is possible by using implantable central venous port systems with a portable disposable pump in an outpatient setting. This study is an evaluation of the usefulness of implantable central venous port systems for colorectal cancer chemotherapy. **Methodology:** An implantable central venous port system was placed in 93 consecutive patients with metastatic colorectal cancer. All patients received modified FOLFOX6 ± bevacizumab or FOLFIRI ± bevacizumab regimens *via* the port system. Follow-up continued for each patient until removal of the port system, death or unavailability of further information. The incidence and details of the complications were investigated retrospectively. **Results:** Out of 1,246 treatments, a total of 16 incidents of port system-related complications were identified (1.28%). Incidents involved infections (n=12), catheter pinch off (n=2), fibrin sheath (n=1) and drug leakage (n=1). A port system removal was required in 14 cases. **Conclusions:** Implantable central venous port systems are safe and have a low long-term complication rate. We consider port systems, such as modified FOLFOX6 ± bevacizumab or FOLFIRI ± bevacizumab regimens, useful for colorectal cancer patients receiving chemotherapy.

Key Words: Central venous port system; Colorectal cancer; Outpatient chemotherapy.

INTRODUCTION

Colorectal cancer (CRC) is the second most frequent cause of cancer-related death in the United States, with an estimated 49,960 deaths in 2008 (1). Approximately 30% of all patients with CRC have metastatic disease at diagnosis and 50% of early stage patients will eventually develop metastatic or advanced disease (2). Most patients with metastatic disease are candidates for systemic chemotherapy to palliate symptoms and prolong life. Significant progress in the treatment of CRC has been achieved with the approval of new drugs. Randomized trials have shown improvements in progression-free and overall survival when irinotecan has been added to infusional fluorouracil and leucovorin (FOLFIRI) in the initial treatment of patients with metastatic colorectal cancer (3). The addition of oxaliplatin to infusional fluorouracil and leucovorin (FOLFOX) increased tumor response rates and disease-free survival (4). Patients receiving all 3 of the key drugs, fluorouracil, oxaliplatin and irinotecan, were noted to have a median overall survival of approximately 20 months (5). Currently, the anti-angiogenic strategy has focused on inhibiting the vascular endothelial growth factor (VEGF) that stimulates blood vessel proliferation. Bevacizumab (Avastin; Genetech, South San Francisco, CA, USA) is a humanized monoclonal antibody directed against VEGF that has been examined in combination with chemotherapy in patients with advanced CRC (6). It is difficult to complete chemotherapy regimens, such as FOLFOX ± bevacizumab or FOLFIRI ± bevacizumab, in an outpatient setting because these regimens are complex and require prolonged continuous intravenous infusions.

A completely implantable subcutaneous central venous infusion port system has been used for the reliable and convenient administration of various therapeutic agents in cancer patients. This port system makes chemotherapy safe for outpatients. However, as noted in previous data, the most common malfunctions included port-associated infection and thrombosis (7). The purpose of this study was to investigate the port system-related complications in outpatient home chemotherapy, such as FOLFOX ± bevacizumab or FOLFIRI ± bevacizumab, for the treatment of CRC.

METHODOLOGY

From May 2005 to the present, port systems were placed in a total of 93 patients for the treatment of CRC chemotherapy. The port system (Groshong catheter, MRI port, Bard, Salt Lake City, UT, USA) was implanted in the subclavian veins. Chemotherapy was performed in the outpatient chemotherapy room using a port system with a portable pump. The location of the catheter tip was placed in the superior vena cava. Information regarding the patient's age, chemotherapy regimens and complications was collected. Follow-up continued for each patient until removal of the port, death, or unavailability of further information.

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RESULTS

Patient characteristics

Ninety-three patients with metastatic CRC were treated by modified FOLFOX6 ± bevacizumab or FOLFIRI ± bevacizumab or sLV5FU2±bevacizumab regimen from May 2005 to April 2009. The patient characteristics are shown in **Table 1**. The patients' ages ranged from 39 to 80 years (median 63 years). A total of 1,246 cycles of treatment were administered with a median of 11 cycles per patient (range 2-48 cycles). Seven hundred and forty-six cycles of modified FOLFOX6±bevacizumab, 422 cycles of FOLFIRI ± bevacizumab and 62 cycles of sLV5FU2 ± bevacizumab were administered. Port system-related complications were identified in 16 patients (**Table 2**). Twenty patients suffered port infection. Two had pinch-off damage of the catheter system and 1 developed a fibrin sheath formation around the catheter. In one case, an individual was given a subcutaneous injection due to port system breakage. The removal of the port system was required in 12 cases. Median duration from port system placement to onset of infection was 451 days with a range of 34-923 days. A microbiological examination identified staphylococcus species as the source of the infection.

TABLE 1. Patient characteristics.

Characteristics		
Age	Median, years	63
	Range, years	39-80
Gender	Male	55 (59.1)
	Female	38 (40.9)
Primary tumor site	Colon	44 (47.3)
	Rectum	49 (52.7)

TABLE 2. Chemotherapy and port system related complications.

Regimen	Cycle of therapy
Total (median, range)	1246 (11, 2-48)
FOLFOX ± bevacizumab	746
FOLFIRI ± bevacizumab	422
sLV5FU2 ± bevacizumab	62
Complications	**No. of incidents (%)**
Port infection	12 (0.96)
Pinch-off damage	2 (0.16)
Fibrin sheath	1 (0.08)
Drug leakage	1 (0.08)

DISCUSSION

Central venous administration of anticancer agents is useful to avoid venous toxicity. The port system is a permanently implantable venous access device consisting of a port body with a silicone membrane and the catheter line itself. Because a port system is completely covered by skin, it is less prone to infections than a non-implantable catheter. A port system is a safe and effective route for the long-term administration of chemotherapy. The following port system-related complications have been reported: catheter damage, catheter pinch-off, fibrin sheath formation, thrombophlebitis, drug leakage and infection (8). The most common complication associated with the use of a port system was infection, followed by thrombosis and dislocation (7). The rate of catheter-related infections in central venous access catheters ranged from 0.6-27% (8). It is necessary to prevent port system infections because catheter-related infections are an important problem in the outpatient setting, contributing to increased patient morbidity and mortality rate. Our results indicated that port systems are safe and have a low long-term complication rate. Port systems are considered to be safe and well accepted by CRC patients receiving chemotherapy.

CONCLUSIONS

Outpatient chemotherapy regimens, such as FOLFOX ± bevacizumab or FOLFIRI ± bevacizumab, which require the use of a port system, are becoming more common. Although the management of chemotherapy for CRC has been facilitated by port systems, it is necessary to reduce port system complications.

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特集　高齢者の機能性消化器疾患

Seminar

5．高齢者の上部消化管術後の消化管運動障害と対策

持木　彫人　　桑野　博行

KEY WORD

●消化管運動
●高齢者
●上部消化管手術
●術後消化管運動障害

SUMMARY

■消化管は空腹期と食後期では異なった収縮波形態を示し，空腹期においては伝播する強収縮波が特徴であり，食後期には連続する律動的な収縮波が特徴である．高齢者の消化管では壁内神経叢の減少が指摘されており，食道運動，胃運動，小腸運動の低下が報告されている．その結果，嚥下障害，消化不良，便秘などの症状を呈する．消化管手術後には一過性の消化管収縮障害が起こり，術後の経口摂取を遅らせる原因になっている．その改善策としては早期の離床，経口摂取開始などがあるが，高齢者など消化管収縮が減弱している症例では，消化管運動亢進薬を必要とする場合がある．

はじめに

平均余命が過去20年で急速に延び，2050年までには65歳以上の人口が現在の2倍なると考えられている．消化管機能は年齢とともに減弱するが，平均寿命が延びると基礎疾患をもつ人々も増えることになり，基礎疾患，合併疾患によって消化管機能も変化する．本稿では正常な消化管収縮をまず概説し，そして消化管収縮の年齢よる変化，さらには上部消化管術後の機能異常と対策を説明する．

正常消化管運動

消化管運動は摂食前後で明らかに異なる2つのパターンに区別され，空腹期収縮と食後期収縮に分類される(図1A)．1つは強収縮波群よりなる空腹期収縮(interdigestive contraction)であり，摂食後10～12時間目より観察される．もう1つは摂食後に収縮力は弱いながらも，規則的に発生する律動的収縮波群の食後期収縮(postprandial contraction)である．

空腹期収縮の特徴はinterdigestive migrating motor contraction(IMMC)と呼ばれ(図1B)，強収縮群が肛門側に90～100分間隔で規則正しく伝播する[1]．約70～80分の休止期を経て，約20分間持続する極めて強い収縮力をもった収縮波群が胃・十二指腸から始まり，小腸を肛門側へと伝播する．その収縮波は各消化管の部位で収縮波形態が異なっている(図1B)．このIMMCは，生理的には食物残渣や腸管内に溜まった胃液・腸液を肛門側へと排出し，次の食事のための準備をする収縮と考えられ，別名housekeeper contractionといわれている．IMMCは4期に分類され，phase Ⅰは休止期，phase Ⅱは不規則な収縮を示す時期，phase Ⅲは15分以上続く最も特徴的な強収縮であり，その収縮波群は肛門側へと伝播する(図1B)．

■もちき　えりと，くわの　ひろゆき(群馬大学大学院病態総合外科)

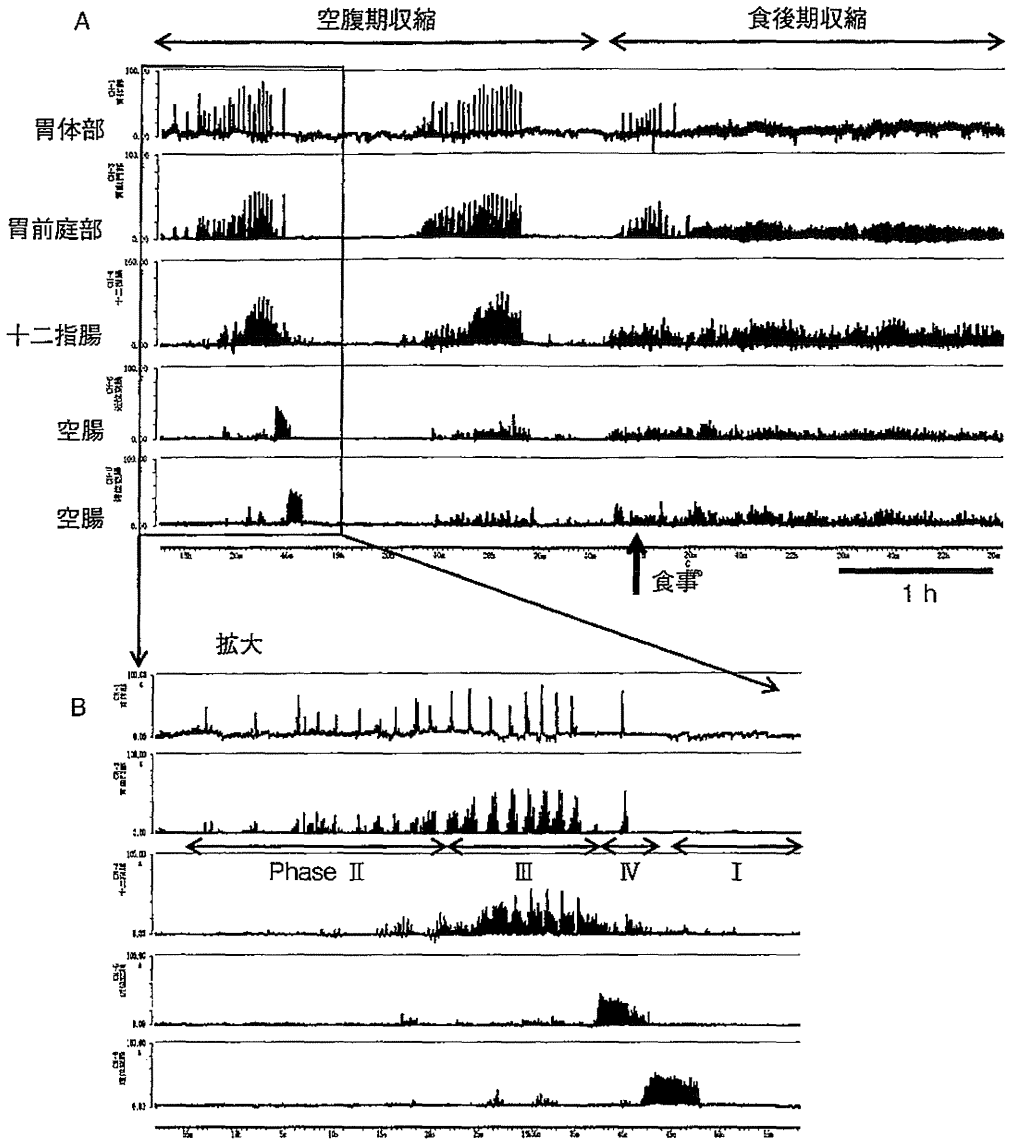

図1　イヌを用いて意識下に測定した消化管運動チャート

A：空腹期から食後期収縮．B：空腹期伝播性強収縮 (IMMC)．横軸が時間軸で縦軸が収縮力を示す．

また，phase Ⅲ後には不規則な収縮で休止期へと移行する減衰収縮を認め，phase Ⅳと分類されている[1]．このIMMCは，十二指腸から上部空腸に存在する消化管ホルモンであるモチリンによって引き起こされており，血中濃度は周期的に変動し，phase Ⅲの時期にモチリンの血中濃度は最高値を示す．

食後期収縮は食事の摂取によって生じる収縮波で，食後3～6時間持続する(図1A)．食事摂取によって，まず胃体部が受容性に弛緩し食物を胃内へと受け入れ，receptive relaxationと呼ばれている．胃体部から胃前庭部の収縮によって食物が徐々に混和，粉砕され，幽門輪を通過する大きさになると十二指腸へと排出される．十二指腸への排出は胃前庭部の収縮，幽門輪の拡大，十二指腸の収縮停止によって調節され，gastro-pyloro-duodenal coordinationと呼ばれている．また，食事摂取に伴って大腸でも収縮が起こり，朝食後の排便などはこの収縮によって惹起され，gastrocolic reflexと呼ばれている．

高齢者の消化管運動

年齢による消化管運動障害の結果として，高

齢者では嚥下障害，消化不良，食欲不振，便秘などが起こるといわれている[2]．食道収縮においては，収縮波高の減少と非伝播性収縮の増加が高齢者で指摘されおり，その結果として嚥下障害が起こる[3]．また，嚥下障害によって誤嚥性肺炎が起きやすくなる．その原因としては食道の壁内神経叢の減少が報告されており，特に食道の口側1/3で顕著とされ，上部食道括約筋の障害も指摘されている[4]．また酸逆流に対するacid clearance低下が，下部食道の収縮力低下や食道裂孔ヘルニアによって起こり，胸焼けや逆流性食道炎の原因となる．

胃の生理的な機能は食物を取り入れ，混和，粉砕し，食物を適当な大きさにして，十二指腸や小腸に送り出すことである．胃の消化管運動に関して，アイソトープを用いた測定で，液体と固体の胃排出が高齢者で遅延していることが報告されている[2]．また，胃電図や^{13}Cを用いた研究では，食後の蠕動や収縮力の低下が指摘されている[5]．原因は未だに明確ではないが，ラットの研究では消化管神経系の変性が原因とされており，特に筋間神経叢でコリン作動性神経に変性が起きていると報告されている[6]．

高齢者の小腸収縮をmanometryを用いて測定した研究では，被験者全員にIMMCが観察されたが，伝播速度が非高齢者に比べて遅いと報告されている[7]．しかし高齢者で診られる吸収障害やbacterial overgrowthは，この消化管収縮障害が原因ではないとも考察している．IMMCの伝播は主に小腸の壁内神経叢によって調節されているが，動物実験では年齢とともに筋間神経叢の神経細胞が減少し，コリン作動性神経の減少や受容体の反応性低下が指摘されており，このような変化が伝播速度の低下につながっていると考えられる[8]．

術後消化管運動障害

開腹手術後には消化管は麻痺になり，一定期間収縮しなくなる．麻痺の原因は腸管の乾燥，腸管への接触，神経系の切除，壁内神経叢の連続性消失，交感神経興奮，体内アミノ酸(グルタミン)の低下などが関係している[9,10]．消化器手術後には消化管収縮は完全に停止した後，小腸から徐々に収縮が回復し，胃，大腸の順に回復する(**図2**)．単開腹だけでも消化管運動の麻痺は起こり，消化管の切除を行うと収縮伝播異常も認められるようになる．

食道切除後には胃管を用いて消化管の再建が行われている．胸腔内に持ち上げられた胃管の機能は，以前は胃管が収縮せず，重力で内容物が落ちると考えられていたが，manometryを用いた研究では前庭部に相当する部位で収縮が確認され，術後の時間経過(年単位)で肛門側から口側に収縮が回復することが確認されている[11]．胃管収縮の機能異常があるときには胃排出遅延が起こり，40～50％の症例で観察されており，迷走神経の離断と胃の小彎側の切除が原因と考えられている．特に高齢者において，食道切除は過大な侵襲になるため，術後の回復も遅く，そのため経口摂取の開始時期も遅くなり，小腸粘膜の萎縮などによって消化吸収能が低下し栄養不良になりやすい．

胃切除術は病変の部位によって切除方法が異なり，機能異常の種類も異なってくる．幽門側胃切除術では幽門輪が切除されるために，急速な胃排出が生じる．また残胃は除神経されているため，収縮せず単なる袋となる．残胃からの排出は，吻合部の状態も重要だが十二指腸運動に依存し，十二指腸収縮が悪いと胃停滞となる(**図3**)．高齢者においては消化管の収縮能が低いため，胃排出遅延が起こりやすい．噴門側胃切除術では，下部食道括約筋(LES)が切除されるため食道逆流が生じ，逆流性食道炎の発生が患者のQOLを低下させる(**図4**)．食道逆流を予防するためには食道と残胃の間に空腸を間置したり，食道-残胃吻合部周囲に残胃を巻き付けて高圧帯を作り，逆流を防止する工夫がされている．噴門側胃切除術では前庭部が残るため，術後の経過とともに残胃の収縮能は改善し，それに伴って食道逆流も減少する．**図4**は噴門側胃切除術・胃管再建後1年の消化管運動でありIMMCが観察され，その収縮波は残胃から十二指腸へと伝播している．胃全摘術はLESも幽

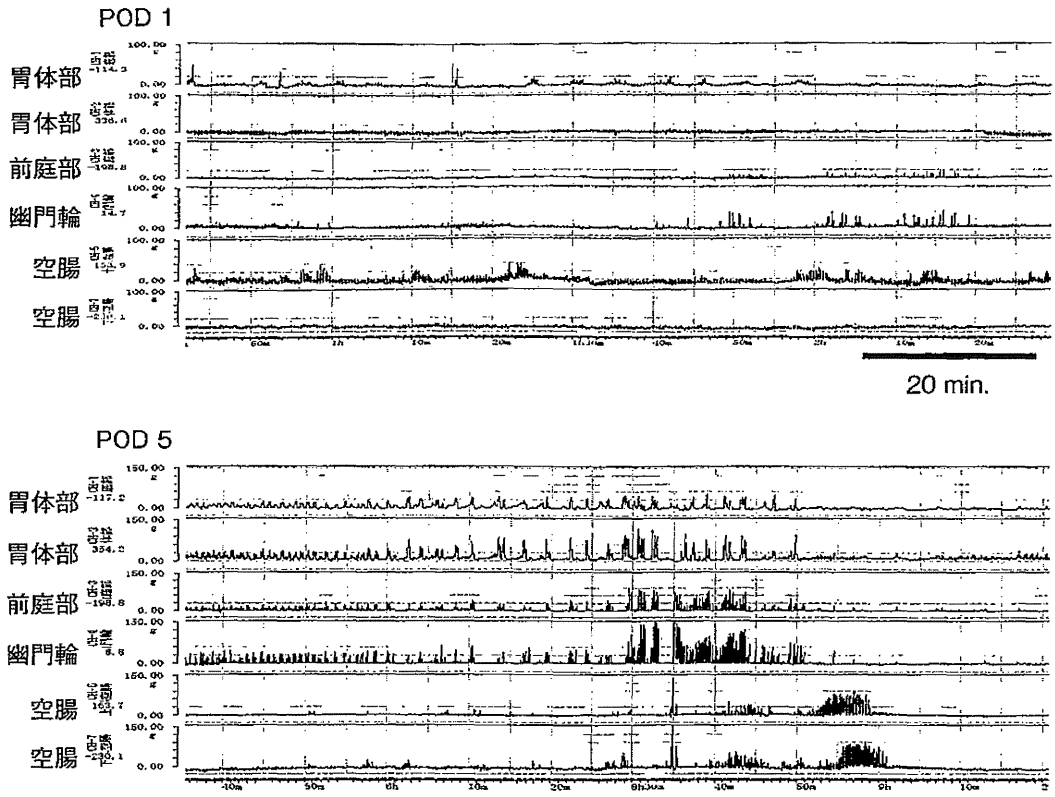

図2

POD 1：開腹手術後1日目の消化管運動．胃から空腸まで収縮が観察されず，完全に消化管運動が麻痺している．POD 5：徐々に消化管運動が回復し，術後5日目になると弱いながらもほぼ正常な IMMC が観察される．

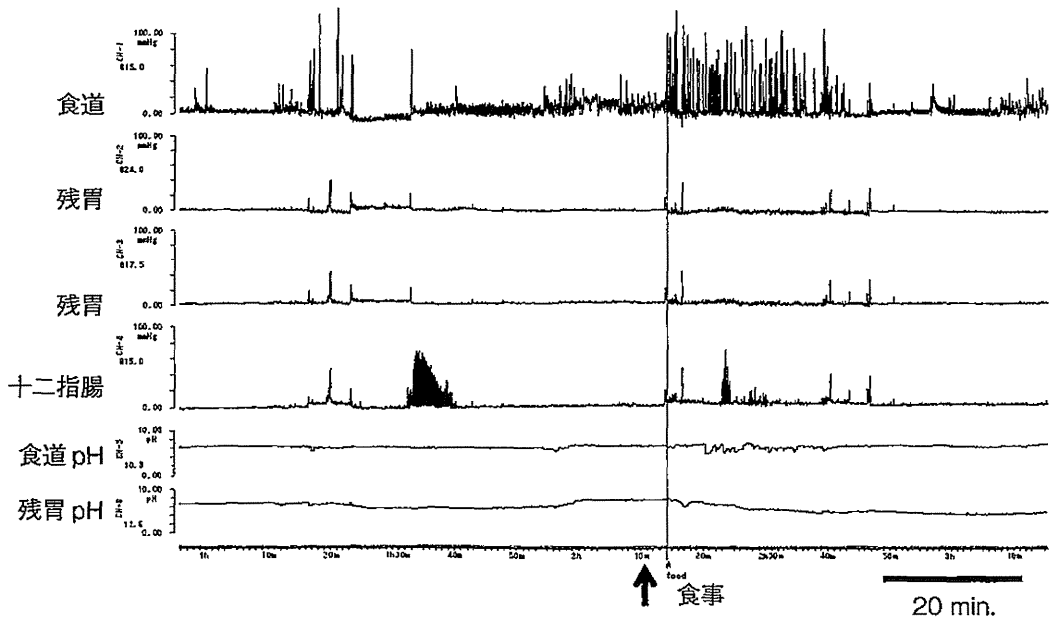

図3　幽門側胃切除術後の消化管運動

残胃は収縮せず，空腹期に十二指腸に phase Ⅲが観察される．残胃内の pH は胃酸が出なくなるため6前後を推移する．

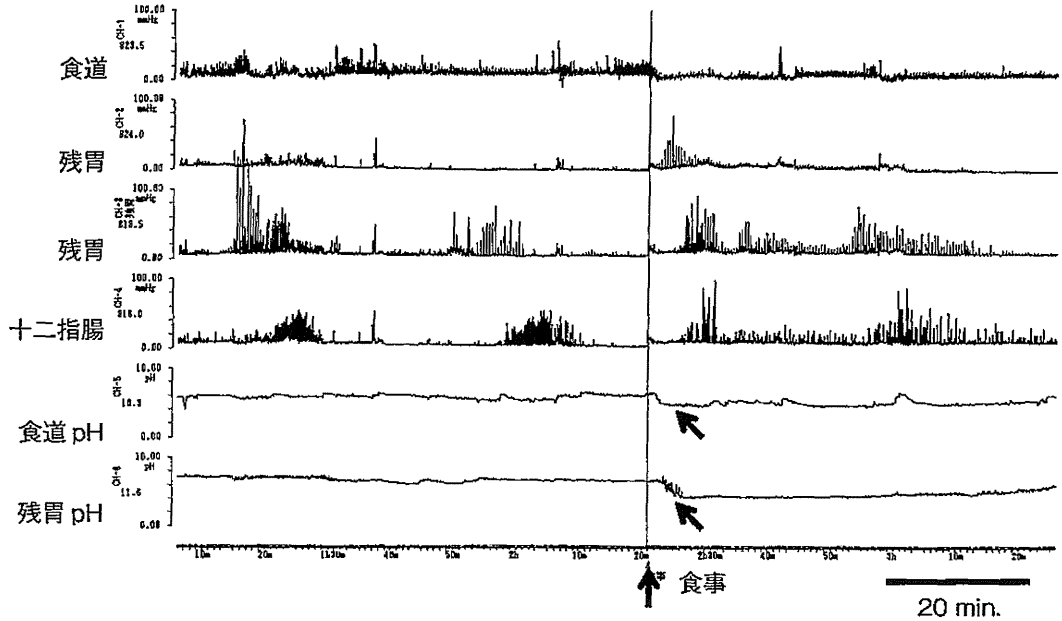

図4　噴門側胃切除術・細径胃管再建術後の消化管運動
食後期には残胃内のpHの低下に伴って食道内pHの軽度の低下が観察され(→)，胃酸の食道逆流が推測される．

門輪も切除され，再建は空腸を用いて行われる．胃全摘術後の再建にgolden standardはないが，Roux-en-Y再建が多くの施設で行われている．本術式は，胆汁や膵液が食道内に逆流するのを防止するのに有効であるが，一部の症例では嘔気や嘔吐，食後に腹部膨満を訴える症例があり，Roux-en-Y stasis syndromeとして知られている[12]．原因は再建腸管に異所性のペースメーカーができるためと報告されており，高齢者に多いという報告はないが，経過観察中に注意する必要がある．胃全摘術によってなくなった貯留能を回復させる目的で，小腸嚢再建術も行われている．しかし小腸嚢再建術は，正常な小腸の輪状筋を離断するため術後の収縮能の回復が遅く，QOLに寄与しないとの報告もあり，高齢者には適応が難しいと考える[13]．

対策

高齢者の術後の消化管運動障害に対しては，まずは術後の早期離床が重要となる．しかし高齢者における早期離床は患者本人だけでは難しく，看護師，家人の協力が必要になる．次に重要なことは早期の経口摂取開始である．多くの論文は早期の経口摂取開始が入院期間を短くして，それによって合併症の発生頻度も増加しないと報告している[14]．一方で，早く始めても，自由に摂取させても結果に変わりはないとの報告もあるが，早期の経口摂取に否定的な報告は見当たらない[15]．しかし高齢者の場合，注意しなければならないのは誤嚥であり，誤嚥性の肺炎を併発すると重篤になり，経口摂取の開始前に水分などによる十分な嚥下のリハビリテーションが必要である．

離床や早期の経口摂取によっても消化管運動機能障害が残る場合には，消化管運動亢進薬の投与が必要になる．術後の運動障害に対してよく用いられた薬は$5HT_4$受容体作動薬であるシサプリド(アセナリン®)であるが，不整脈の副作用により現在は使用できない．その代替品としてはモサプリド(ガスモチン®)があるが，医療保健上の適応は慢性胃炎である[16]．術後にシサプリドを用いた報告では食道逆流を減少させ，また術後の腸閉塞発症を予防するとの報告がある[17]．漢方である大建中湯も術後の腸閉塞を予防すると報告されている[18]．大建中湯は山椒，人参，生姜から成る生薬であり，日本独自の漢方薬である．作用機序としては，コリン作

III 副作用各論—重大な副作用—

皮　膚

手足症候群

Hand-foot syndrome

浅尾高行　　桑野博行

Key words：皮膚障害，手足症候群

1 概念・定義

抗がん薬によって引き起こされる皮膚の急性病変で，手掌，足底を中心とした紅斑，腫脹，過角化，色素沈着などを特徴とする症候群である．抗がん薬による表皮細胞への直接的障害に外的な機械的刺激が加わって発症，増悪する病態と考えられる．顔面のざ瘡様皮疹や爪甲の変化など薬剤の種類によっては特徴的な病変を伴うこともあり，必ずしも手足に限るものではない．

しかし，最近では休薬を余儀なくされるような手足症候群を引き起こす薬剤が広く使用され[1-3]，手足症候群は抗がん薬治療中の患者のQOLの維持だけでなく，抗がん薬治療全体としての成績にかかわる重要な有害事象として認識されるようになった．

2 原因薬剤

フッ化ピリミジン系薬剤ではカペシタビンが高頻度に手足症候群がみられる薬剤として知られている．テガフール・ギメラシル・オテラシルカリウムやテガフール・ウラシルでも認められるが発生頻度は低い．ドキソルビシンやタキサン系抗がん薬ではフッ化ピリミジン系薬剤による手足症候群と同様の皮膚症状が生じる．

フッ化ピリミジン系薬剤による手足症候群は比較的びまん性に生じ皮膚が菲薄化するのが特徴であるのに対して，キナーゼ阻害薬(EGFR阻害薬)による皮膚病変は，限局性で角化が強い傾向がある．

抗EGFR抗体のセツキシマブ，パニツムマブでは顔面や上半身を中心にざ瘡様の皮疹や，爪周囲炎など特徴的な皮疹が高頻度に認められる．

このような，薬剤による皮疹の特徴を把握し特有の初期症状を見逃さないように留意する必要がある．

3 発生機序

フッ化ピリミジン系薬剤による手足症候群では，皮膚基底細胞の増殖阻害，エクリン汗腺からの薬剤分泌，5FUの分解産物が発生に関与しているという報告があるが確定的な発症機序は不明である．なぜ，手と足に起こりやすいかについても様々な推察がなされてきたが，信頼できるデータはない．機械的な刺激が発症の契機や増悪因子となることから，手や足は物理的な刺激を受けやすい部位であることが少なからず関与していると思われる．抗EGFR阻害薬では，抗腫瘍効果であるEGFR阻害作用が正常の皮膚

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にも作用して皮膚障害を誘発すると考えられる．ケラチノサイトのアポトーシスが誘導されると同時に，ケモカインを介して炎症細胞が動員され各種皮膚症が引き起こされる．

4 症状，診断法

1) 初期症状

手足症候群の好発部位は，反復した物理的刺激が起こる場所で必ずしも手足に限らない．早期発見のポイントは，感覚の異常，発赤の有無を頻繁に確認し初期症状を見過ごさないことである．急性の有害事象であり投与後早期に出現することが多いので，症状の発現頻度や発現時期について投与前からよく説明して予防的ケアと患者教育を行っておく．軽微な症状の場合には患者は気がついていても訴えないことがあるので，診察時には皮膚を詳細に観察するとともに医療者側も多職種で連携して早期対処に心がける．

a. フッ化ピリミジン系薬剤による手足症候群の初期症状

発症早期には，しびれ，チクチクまたはピリピリするような感覚の異常が認められる．この時期には視診では手足の皮膚に変化を伴わない．最初にみられる皮膚の変化は比較的びまん性の発赤(紅斑)である．進行すると皮膚表面に光沢が生じ，指紋が消失するようになる．

b. 抗EGFR阻害薬による初期症状

手足では限局性の紅斑で始まることが多く，通常，疼痛を伴い皮膚は肥厚する．フッ化ピリミジン系薬剤による手足症候群と初期皮膚所見が異なる場合があるので注意を要する．進行すると水疱を伴い疼痛も強くなる．

抗EGFR抗体では投与後1週間以内に紅色丘疹または膿疱性の丘疹が顔面，前胸部，背部を中心に認められる．

2) 所　見

手足症候群の皮疹は多彩で以下のような所見が混在してみられることが多いが，薬剤により特徴がある．

a. 紅斑・腫脹

手掌～手指，足底～足趾にびまん性の紅斑が出現し，多少とも浮腫性に腫脹する．皮膚表面はやや光沢を帯び，指腹の指紋が消失する傾向がある．キナーゼ阻害薬による紅斑は限局性のことが多い．

b. 色素沈着・色素斑

手掌，足底にびまん性に褐色の色素沈着を生じ，関節背面や爪周囲にも色素沈着を伴う．

c. 過角化(角質増生)・落屑・亀裂

手掌，足底の角層が肥厚し，表面が硬く触れるようになる．角層が剥離して，落屑を生じることも多い．指尖，踵などの過角化部や指関節屈曲部などの皮膚表面にしばしば亀裂を生じ，疼痛を伴う．

d. 水疱・びらん・潰瘍

進行すると表皮下水疱を生じ更に強い疼痛を訴えるようになる．水疱が破れると，びらん・潰瘍化し，出血や痂皮を伴う．

e. 爪甲の変化

爪甲に変形，粗造化，混濁，萎縮や色素沈着を生じる．肥厚した爪甲は薄く剥がれてくる．高度になると爪甲の脱落も起こる．

f. 爪 囲 炎

陥入爪のように肉芽を生じると，痛みを伴い日常生活に支障をきたす．投与を開始してから2-3カ月後にみられる所見である．

g. ざ瘡様皮疹

顔面や前胸部を中心に，思春期にみられるざ瘡に似た皮疹であるが無菌性である．抗EGFR抗体製剤で高頻度にみられる．

h. 皮膚乾燥症

手足だけでなく体幹部にも広範囲に皮脂の減少と乾燥が進みdry skinとなる．特に冬にはかゆみを伴う．

i. 光線刺激による皮疹

日光刺激による発赤，腫脹をきたす．日差しが強くなる夏に多く発症し，日光が当たる前額部，目の下に強い'日焼け'のような発赤が生じ痛みを伴う．

3) グレード判定基準

グレード判定は休薬や投薬の再開の基準とな

表1 Blumのグレード分類(手足症候群 Hand-Foot Syndrome Atlas, 第3版より引用)

はっきりした疼痛を伴う場合はグレード2以上と判定するが,チクチク感など表面的な皮膚知覚異常はグレード1とする.痛みが強く日常生活が遂行できない状態であればグレード3となる.具体的には手では「ペンや箸が使えない」,足では「歩くのが困難」などを指標として判断する.

グレード	臨床領域	機能領域	(参考)判定基準にない具体的症状例
1	しびれ,皮膚知覚過敏,ヒリヒリ・チクチク感,無痛性腫脹,無痛性紅斑,色素沈着,爪の変形	日常生活に制限を受けることのない症状	(対処の必要ないもの)皮膚,爪の色素沈着,爪の変形 (対処の必要なもの)皮膚の硬化感
2	腫脹を伴う有痛性皮膚紅斑,爪甲の高度な変形・脱落	日常生活に制限を受ける症状	爪症状(脱落など痛みを伴うもの)
3	湿性痂皮・落屑,水疱,潰瘍,強い痛み	日常生活を遂行できない症状	爪症状(機能障害あり)

該当する症状のグレードが両基準(臨床領域,機能領域)で一致しない場合は,より適切と判断できるグレードを採用する.

この基準は判定のみに採用され,他の皮膚症状,他部位の皮膚の評価には用いない.

※色素沈着について:色素沈着に対する対処法は確立しておらず,また,グレード2,3(痛みや機能障害)へと進行するものではないため,対処(処置)の必要はないと考えられる.

有害事象共通用語規準(v3.0日本語訳JCOG/JSCO版)

グレード	手足皮膚反応
1	疼痛を伴わない軽微な皮膚の変化または皮膚炎
2	機能障害のない皮膚の変化または疼痛
3	潰瘍性皮膚炎または疼痛による機能障害を伴う皮膚の変化
4	—(設定なし)

るので,正確な判定が不可欠である.判定基準は皮膚所見をみる臨床領域と日常生活制限の程度をみる機能領域から判定するBlumの分類[4]が理解しやすく一般的に用いられている.手足症候群の評価は医療者側の判定のばらつきが大きくなりがちである.判定には痛みや日常生活の制限の程度が判断の基準になることから,具体的な症状と機能障害程度を正確に聴取する.生活の障害の程度は,手の障害であれば,箸や鉛筆が使えない,ボタンがかけられない,足であれば歩行ができないなどを指標とする(表1).

4) 臨床検査値

手足症候群の発生と因果関係のある臨床検査値異常は報告されていない.

5 対処法

手足症候群の治療法と予防法は確立していないため,確実な処置は原因薬剤の休薬である[5].適切なタイミングでの休薬と再開が患者のQOLと治療の継続を左右する.重篤化を防ぐには早期診断と適切な初期対応が重要であり,そのために詳細な症状の聴取と皮膚の観察が基本となる.皮膚だけでなく,爪,毛髪にも変化がみられるので見逃さないようにする.皮膚症状は多彩であるが,視診で診断可能な病変であり,患者自身が症状の発見や病状の推移を観察することができるので自己管理,自己ケアが有効な有害事象である.手足症候群では投与後初期に発症するものが多いので,投薬開始前に,予想さ

表2 日常生活の指導の実際(文献[6]より引用)

①物理的刺激を避ける	締め付けの強い靴下を着用しない
	足にあった柔らかい靴をはく
	エアロビクス，長時間歩行，ジョギングなどの禁止
	包丁の使用，ぞうきん絞りを控える
	炊事，水仕事の際にはゴム手袋等を用いて，洗剤類にじかに触れないようにする
②熱刺激を避ける	熱い風呂やシャワーを控える
③皮膚の保護	保湿剤を塗布する
	木綿の厚めの靴下をはく
	柔らかい靴の中敷を使用する
④2次感染予防	清潔を心がける
⑤直射日光にあたらないようにする	外出時には日傘，帽子，手袋を使用する
	露出部分にはサンスクリーン剤を使用する

れる症状や予防的なケアについて患者や家族に伝えて指導を行う．

1) 皮膚症状の発生・増悪因子

手足症候群は抗がん薬の皮膚の細胞への障害を背景として，皮膚に対する外的な刺激が加わって発症するので皮膚障害の発生誘因，増悪因子の排除が重要である．刺激としては機械的刺激や，温度刺激，光線による刺激が想定される．想定される増悪因子をあらかじめ取り除いて，皮膚に対する刺激を軽減させることが予防的ケアと発症後の治療のどちらにも共通した原則となる．皮膚のケアの具体的方法は，刺激の排除，清潔の保持，保湿にまとめられる．

2) 皮膚への刺激の排除

重篤副作用疾患別対応マニュアル(厚生労働省[6])には生活上の注意点として刺激別に具体的に記載されている(表2)．物理的刺激が生じやすい部分を問診により確かめ，同じ部位に刺激がかからないように患者の生活状況に即した対応を個別に指導する．

3) 清潔の保持

感染の合併を防ぐためにも皮膚を清潔に保つ．入浴では熱い湯や刺激の強いタオルでの摩擦を避け，低刺激の弱酸性石鹸の使用を指導する．手に比べて洗う機会が少ない足のケアとして，足浴が勧められる．また，爪の手入れ，厚い角質の除去などもあらかじめ行っておく．手湿疹(主婦湿疹)や白癬症との鑑別診断が必要になることがあるので，あらかじめ評価，治療しておく．

4) 保　湿

手足症候群を引き起こす抗がん薬の多くは，皮脂腺や汗腺にも障害を及ぼし，皮膚のバリア機能が損なわれる．dry skinの状態は表皮細胞への外的刺激を増長する．抗がん薬の投与開始後と同時に軟膏の塗布を開始する．ワセリンで代表される軟膏は油脂の中に水が懸濁分散したもので，べとつき感が強くつけ心地が悪いため患者の受け入れはよくないが，付着性が良く効果が持続することと浸潤部にも用いることができる利点がある．これに対して水溶成分に油脂を懸濁分散させたクリームやローションはつけ心地が良い反面，落ちやすく効果は持続しない．皮膚保護，保湿効果を優先し基本的に軟膏を用いるが，患者の受容性も考慮して軽症例あるいは予防的使用にはクリームが代用されることもある．この場合にも重症になれば軟膏に変更する．製品名が軟膏となっているものも成分はクリームのことがあるので注意が必要である．1日1回の保湿ケアでは不十分であり1日数回，定時の塗布を指示する．残りの軟膏のチューブを持参させるなどして軟膏の消費量からコンプ

ライアンスを評価する.

5) 休薬・減量

皮膚の症状は基本的に蓄積毒性ではないので,休薬が有効である.原則としてGrade 2以上で,休薬あるいは減量が適応となり,再開時には再発を避けるためにGrade 1に回復してから薬剤を減量して投与する.早期に対応しGrade 3にしないことが重要である.休薬・減量基準は,薬剤ごとに細かく決められているのでそれぞれの薬剤の副作用対応マニュアルなどを参考にする.

6) 局所療法

外的な刺激を除くことに加えて重症度に合わせて,消炎,抗菌療法を付加する.副腎皮質ステロイド軟膏は,吸収が良い顔面では,体幹より1ランク弱いものを用いる.その他の部位ではvery strongランクの副腎皮質ステロイド軟膏を使用する.ビタミン剤や抗炎症薬の全身投与については,明らかな有効性を支持するデータはない.特徴ある症状に対する対処法を以下に示す.

a. ざ瘡様皮疹への対処法

抗EGFR抗体により顔面,胸部にみられる特徴的な皮疹で,ざ瘡に似ている.発現時期は投与後早期にみられ,87%にみられることから投与と同時に予防的に治療を開始する.予防としては保湿剤とテトラサイクリンの内服を開始し,症状の出現とともに,副腎皮質ステロイド軟膏を使用する.思春期にみられるざ瘡と異なり無菌といわれているが,テトラサイクリンの内服が有効である.これは,抗菌作用以外に抗炎症作用をもつためとされている.重症化しGrade 3となると副腎皮質ステロイドの内服,抗EGFR抗体のスキップや減量が必要となる.

ざ瘡様皮疹が消退すると皮膚は荒廃し,皮膚の乾燥(乾皮症)が進行するので,保湿クリームにて対処する.

b. 爪囲炎への対処法

爪は刺激から皮膚を守る機能をもっているが,同時に,爪の外側に接した皮膚に外力がかかると爪が皮膚刺激となり炎症が起こる.爪囲炎は,抗EGFR抗体でも高頻度に認められる副作用である.投与開始数週間後に出現し慢性の経過をたどり対応に苦慮することが多い.爪周囲に限局性の皮疹がみられたら,減圧処置を行うとともに2次感染を予防しながら軟膏処置を行う.爪囲炎を放置すると,慢性の肉芽を生じ痛みのため歩行障害をきたし陥入爪に似た所見を示す.腫脹がある場合には副腎皮質ステロイド軟膏を使用し,感染を伴う場合には抗生剤の内服を行う.足の母趾にみられることが多いが手の爪にも生じる.機械的刺激を避けるには,爪の手入れと爪に接する皮膚にかかる圧力を減圧する.指の側面の皮膚を外側に引っ張るスパイラルテープ法[7]が有効である.通常の外傷のようにテープを巻くと爪が皮膚に食い込む方向に力がかかり悪化することがあるので注意する.

c. 皮膚潰瘍・亀裂への対処法

かかとや指先に亀裂や皮膚の欠損が生じると痛みが強く機能障害を引き起こす.もともと皮膚の細胞修復機能の障害が背景にあるので,創の湿潤環境を整え修復機転を促す処置が必要となる.局所療法として創の洗浄に加えてゲル状の皮膚保護剤が痛みの軽減にも治療にも有効である.保護剤の材質が厚く硬いと辺縁での機械的刺激を生じるため,デュオアクティブ®ETなどの追従性の良い薄型で柔らかい素材のドレッシング材を使用する.尿素軟膏は刺激が強いので皮膚の欠損を伴う場合には使用しない.症状に応じて休薬や副腎皮質ステロイド軟膏が必要となる.

おわりに

直接生命にかかわるほど重篤になることはない有害事象ではあるが,重症化すれば患者QOLの低下を引き起こし,間接的に患者の生命予後を左右することもありうることは銘記すべきである.

2. 頸部食道癌に対する機能温存目的のneo-adjuvant therapy*

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〔要旨〕術前化学放射線療法の進歩は，頸部食道癌における喉頭温存可能例の増加をもたらしている．頸部食道癌治療において，根治性を損なわず，なおかつ発声や嚥下といった喉頭機能を温存するということは大きな課題であり，治療適応の慎重な検討と選択，複雑な解剖を正確に理解することと，確実な手技が必要である．本稿では，頸部食道癌に対する機能温存目的のneo-adjuvant therapyとそれに続く手術療法について概説する．

はじめに

頸部食道は上部消化管のうち，輪状軟骨下縁から胸骨切痕までの10 cm程度を占める狭い領域である．頭側には下咽頭・喉頭，前面には気管・甲状腺，左右には反回神経，総頸動脈，内頸静脈，迷走神経，上皮小体が位置する．頸部食道癌は進行癌として発見される頻度が高く，こうした周囲臓器への浸潤の程度や多発病変の有無によって治療法を選択する必要がある．根治切除に際して喉頭の合併切除が必要となる場合，発声機能を失うこととなり，大きなquality of life (QOL)の低下を招く．喉頭が温存された場合でも，術後に嗄声や誤嚥を生じることが少なくない．本稿では，頸部食道癌に対する機能温存目的のneo-adjuvant therapyと，それに続く手術療法について概説する．

Ⅰ．喉頭機能温存のための術前化学放射線療法(CRT)の目的

頸部食道癌に対し喉頭温存手術が適応となるのは，『食道癌診断・治療ガイドライン』(2012年4月版)[1]によると，喉頭・気管に腫瘍浸潤がなく，腫瘍口側が食道入口部より下方にとどまる症例である．また，喉頭摘出の回避の可能性を高めるために，喉頭合併切除の手術適応となる頸部食道癌例に対して，術前あるいは根治的な化学放射線療法は，推奨できるだけの十分な根拠はないが行われることがあると述べられている[1]．われわれは，頸部食道癌における喉頭温存をめざした術前CRTを行い，腫瘍の縮小によって喉頭・気管への浸潤を解除し，腫瘍口側に吻合するための十分なマージンを確保することで，機能温存をめざしている[2~8]．

キーワード：頸部食道癌，機能温存，neo-adjuvant therapy

* Neo-adjuvant therapy of cervical esophageal cancer for larynx-preservation

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