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exposure is a major risk.[14,15] Paclitaxel is effective for treatment of malignant ascites from gastric cancer,[16] and in studies[17,18] of paclitaxel for the second-line chemotherapy, it was especially effective for peritoneal metastasis. Fluoropyrimidine monotherapy has been used for adjuvant chemotherapy in Asia, and a combination of tegafur and uracil (UFT) was for a time the Japanese community standard treatment for gastric cancer because of its efficacy, good compliance, and safety.[5] In 2007, the NSAS-GC study[19] showed that UFT plus surgery was more effective than surgery alone for Japanese patients who had had a D2 dissection for T2 and lymph node positive gastric cancer. UFT has since been replaced by S-1 in Japan because of the results of ACTS-GC,[3] which was a large randomised controlled trial for stage II and III tumours, although no direct comparison of these two drugs has been done. Combination of paclitaxel and oral fluoropyrimidine is a candidate treatment for curatively resected gastric cancer at high risk of peritoneal recurrence (ie, serosa-positive tumours).[14] However, no comparison has been done of concurrent and sequential regimens. Because of the poor nutrition of patients after gastrectomy[20] and the interaction between paclitaxel and fluorouracil,[21] we tested the effect of sequential paclitaxel followed by S-1 for locally advanced gastric cancer in the single group trial,[22] with favourable results.

We did the Stomach cancer Adjuvant Multi-institutional group (SAMIT) trial for T4a or T4b[23] gastric cancer to assess (1) the effect on survival of paclitaxel followed by oral fluoropyrimidine (sequential treatment) compared with fluoropyrimidine alone (monotherapy), and (2) the non-inferiority of UFT compared with S-1.[24]

Panel 1: Eligibility criteria

Inclusion criteria

- Histologically proven gastric adenocarcinoma
- Clinical stage including surgical findings: T4a–b, N0–2, P0, H0, and M0
- D2 or equivalent dissection done, and macroscopically no residual disease (R0 or R1 including lavage cytology 1 or X)
- No previous chemotherapy or radiotherapy
- Age 20–80 years
- Preoperative Eastern Cooperative Oncology Group performance status of either 0 or 1
- Sufficient main organ function
- Able to start chemotherapy 14–56 days after surgery
- Without active synchronous cancer

Exclusion criteria

- Serious concomitant disease
- History of serious drug hypersensitivity
- Acute inflammatory disease
- Pregnant, possibly pregnant, or lactating
- Other active cancer that may affect survival or adverse events
- Determined by the investigator to be unsuitable for other reasons

Methods

Study design and participants

We did this phase 3, randomised controlled study at 230 hospitals in Japan. We used a two-by-two factorial design, with four treatment groups: UFT alone, S-1 alone, paclitaxel followed by UFT, and paclitaxel followed by S-1. This design enabled us to evaluate the superiority of sequential treatment compared with monotherapy as well as the non-inferiority of UFT compared with S-1. The design of the study has been described previously.[24]

Panel 1 shows the eligibility criteria. In the original protocol, the control group for the non-inferiority comparison was 24 weeks of UFT. However, following the results of ACTS-GC, showing the effectiveness of 1 year of adjuvant S-1 compared with surgery alone, the control group was changed to 48 weeks of S-1 through a protocol amendment dated May 10, 2007. The non-inferiority margin for S-1 was initially set as 1·25; however, in ACTS-GC, the risk reduction of recurrence-free survival by S-1 was 0·62, therefore the data and safety monitoring committee approved changing the margin to 1·33.

The trial was approved by the institutional review board of each participating institution and done in accordance with the Declaration of Helsinki. All patients provided written informed consent before or after surgery.

Randomisation and masking

Randomisation was done centrally and independently at the non-profit organisation Epidemiological and Clinical Research Information Network (Okazaki, Japan). The minimisation method was applied to obtain a balance for tumour size (<8 cm *vs* ≥8 cm), lymph node metastasis (positive *vs* negative), and study site. A unique random sequence was generated before the enrollment by an independent statistician and sequentially applied to each patient's allocation. The detailed procedures of randomisation were not disclosed to researchers at the participating sites. Participants, investigators, and other staff were not masked to treatment allocation.

Procedures

Gastrectomy was only done by laparotomy—laparoscopy was not permitted. Immediately after opening the abdomen, the investigator had to search for tumours in the abdomen by visual inspection and palpation. Gastrectomy by laparotomy had to be attempted first if oesophageal invasion was less than 3 cm, irrespective of thoracotomy. Peritoneal cytology was not necessary for enrolment purposes but was done according to the usual policy of each institution where performed. Tumour exposure to serosa or adjacent invasion, T4a or T4b, was assessed during surgery for clinical staging. Because tumour size is related to prognosis,[25,26] the size was determined macroscopically in surgical specimen.

In the UFT only group, patients were given oral UFT 267 mg/m² in two or three doses per day, for 28-day courses for 48 weeks. In the S-1 only group, patients were given S-1 80 mg/m² orally twice per day for 14 days followed by 7 days rest for 48 weeks. In the paclitaxel then UFT group, patients were given an intravenous infusion of paclitaxel 80 mg/m² administered over 1 h on days 1 and 8, followed by a 1-week rest beginning on day 15 in course 1 (21 days), and on days 1, 8, and 15 followed by a 1-week rest from day 22 following courses 2 and 3 (28 days), for 11 weeks. Patients then received nine courses (36 weeks) of UFT 14 days after the last infusion of paclitaxel. In the paclitaxel then S-1 group, three courses (11 weeks) of paclitaxel treatment, and 12 courses (36 weeks) of S-1 were given.

The protocol treatment was discontinued for the following reasons: (1) recurrence or death, (2) withdrawal of consent, (3) protocol violation or ineligibility, (4) a pathological finding of intramucosal cancer, (5) investigator's discretion, (6) adverse events: more than 29 days of unresolved events that prevent starting or continuing a course, more than two dose reductions needed, grade 3 hypersensitivity reaction, or grade 4 non-haematological toxic effect. Criteria for continuation of treatment included white blood cell count at least 3000 per mL or neutrophil counts at least 1500 per mL; platelet count at least 75000 per mL; serum creatinine concentration no more than 1·5 mg/L; alanine aminotransferase and aspartate aminotransferase concentrations no more than 100 IU; no worse than grade 1 nausea, vomiting, diarrhoea, or stomatitis; performance score 0–1; other non-haematological toxic effect no worse than grade 2; body temperature less than 38°C.

Toxic effects were assessed with the Common Toxicity Criteria for Adverse Events (version 3.0), with a defined protocol for modifications and delays (appendix). All patients were followed up until death or until 3 years after the last patient enrolled. During treatment, patients physical and blood examinations were done every 1–4 weeks. During and after protocol treatment, patients were physically checked for recurrence every 3 months for 3 years. Abdominal CT or ultrasound scans were done every 3 months in the first 2 years after assignment and every 6 months thereafter.

See Online for appendix

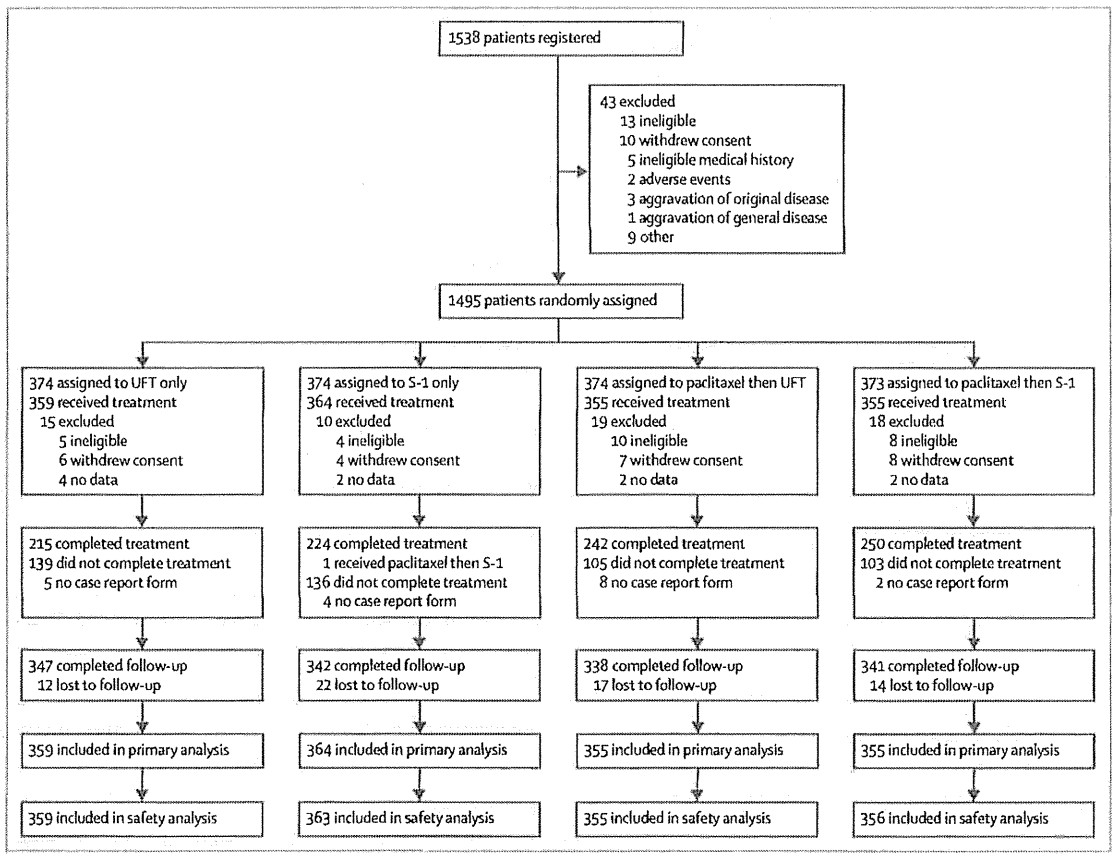

Figure 1: **Trial profile**
One patient assigned to S-1 only received paclitaxel followed by S-1: they were analysed by intention to treat for the primary analysis and per protocol for the safety analysis.

Data were collected and quality checked centrally at the Epidemiological and Clinical Research Information Network data centre. Quality control was done with CluePoints (version 1.2). No atypical data patterns that would affect the analysis were found.

Outcomes

The primary endpoint was disease-free survival, defined as the time between randomisation and the first event (all-cause death, relapse of stomach cancer, or occurrence of a second cancer). The secondary endpoints were overall survival, incidence of adverse events, and proportion of patients who completed the protocol treatment. Overall survival was defined as time between randomisation and all-cause death. Patients who had not had an event were censored at the last follow-up date. All outcomes were assessed for the intention-to-treat population, which included all patients except those who did not receive any treatment at all, who were ineligible after randomisation, or who withdrew consent.

Statistical analysis

We calculated the sample size assuming 3-year disease-free survival of 50% for the monotherapy group, and accrual and follow-up periods of 3 years. We calculated that 1480 patients (370 per treatment group) were needed to achieve 90% power to reject the null hypothesis of an equal chance of disease-free survival with sequential treatment and monotherapy at a two-sided significance level of 5%, assuming that the risk reduction in the sequential treatment group would be 20% and that 5% of patients would be lost to follow-up. This sample size would also provide 88% power to show the non-inferiority of UFT compared with S-1, using a non-inferiority margin of 1·33. We did no interim analyses.

Before the primary analysis, we tested the independence of the two hypotheses with a stratified Cox regression model for the primary endpoint including a corresponding interaction term, and then did the primary analysis if we detected no statistically significant interaction. We compared groups for the primary outcome by stratified log-rank statistics. We estimated the hazard ratio (HR) and its two-sided Wald-type 95% CI with the stratified Cox regression model, stratified by tumour size (<8 cm *vs* ≥8 cm) and N (N0 *vs* N1–2). We tested non-inferiority with a one-tailed Wald statistic. We assessed time-to-event endpoint with the Kaplan-Meier method. No statistical adjustment to control the overall type I error rate was needed because of the two-by-two design.

We did prespecified exploratory analyses of pairwise treatment comparisons with Cox regression models, adjusted using Bonferroni's method. We produced forest plots for subgroup analyses based on the patients' characteristics for disease-free survival and overall survival. Because the protocol was amended to increase the duration of oral drug treatments on May 10, 2007 (from 24 weeks to 48 weeks for monotherapy group, and from 12 weeks to 36 weeks for sequential treatment group), we assessed whether treatment effects on disease-free survival were different before and after the amendment.

We used a significance level of 5%. We did the statistical analyses with SAS (version 9.3) and produced forest plots with Stata (version 12).

This trial is registered at UMIN Clinical Trials Registry, number C000000082.

	UFT only (n=359)	S-1 only (n=364)	Paclitaxel then UFT (n=355)	Paclitaxel then S-1 (n=355)
Tumour size				
≥8 cm	246 (69%)	247 (68%)	241 (68%)	240 (68%)
<8 cm	113 (31%)	117 (32%)	114 (32%)	115 (32%)
Lymph node metastasis				
Positive	305 (85%)	309 (85%)	302 (85%)	301 (85%)
Negative	54 (15%)	55 (15%)	53 (15%)	54 (15%)
Sex				
Women	109 (30%)	120 (33%)	119 (34%)	105 (30%)
Men	250 (70%)	244 (67%)	236 (66%)	250 (70%)
Age (years)				
≥65	187 (52%)	186 (51%)	198 (55%)	192 (54%)
<65	172 (48%)	178 (49%)	157 (44%)	163 (46%)
Eastern Cooperative Oncology Group performance status				
0	317 (88%)	314 (86%)	301 (85%)	302 (85%)
1	42 (12%)	50 (14%)	54 (15%)	53 (15%)
Pathological stage*†				
IA or IB	18 (5%)	15 (4%)	20 (6%)	19 (5%)
II	72 (20%)	90 (25%)	79 (22%)	77 (22%)
IIIA	132 (37%)	128 (35%)	126 (35%)	123 (35%)
IIIB	91 (25%)	94 (26%)	94 (26%)	92 (26%)
IV	40 (11%)	35 (10%)	33 (9%)	40 (11%)
Lavage cytology 1	26 (7%)	29 (8%)	24 (7%)	27 (8%)

Data are n (%). *Recorded according to the Japanese Classification of Gastric Carcinoma.[17] †Data missing for 15 patients.

Table 1: **Baseline characteristics**

Role of the funding source

The funder participated in study design, data collection, and data management, but had no role in data analysis or data interpretation, or the writing of the report. The corresponding and the first authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 3, 2004 and Sept 24, 2009, 1495 patients were randomly assigned to a treatment group (figure 1). 62 patients were excluded because of ineligibility (n=27), withdrawal of consent (n=25), or no data (n=10). 1368 (96%) patients were followed up. Baseline characteristics were well balanced between the four treatment groups (table 1). Full protocol treatment was completed by 215 (60%) of 359 patients in the UFT only

group, 224 (62%) of 364 in the S-1 only group, 242 (68%) of 355 in the paclitaxel then UFT group, and 250 (70%) of 355 in the paclitaxel then S-1 group. The median number of treatment courses was 6 (IQR 4–6) in the UFT only group, 8 (IQR 6–10) in the S-1 only group, 6 (IQR 6–10) in the paclitaxel then UFT group, and 7 (IQR 7–12) in the paclitaxel then S-1 group.

Median follow-up was 62·5 months (IQR 48·3–80·7) for UFT only, 62·8 months (47·9–80·5) for S-1 only, 65·5 months (48·7–81·0) for paclitaxel then UFT, and 61·3 months (47·8–78·9) for paclitaxel then S-1. For the primary endpoint, 728 events had occurred and 592 (41%) patients had died at the time of analysis.

Disease-free survival at 3 years with monotherapy was 54·0% (95% CI 50·2–57·6) and with sequential treatment was 57·2% (95% CI 53·4–60·8), with no significant difference between the two groups (HR 0·92, 95% CI 0·80–1·07, p=0·273; figure 2A). Disease-free survival at 3 years for patients given UFT was 53·0% (95% CI 49·2–56·6) and for those given S-1 it was 58·2% (95% CI 54·4–61·8; HR 0·81, 95% CI 0·70–0·93, p=0·0048; $p_{non\text{-}inferiority}$=0·151; figure 2B). Figure 3 shows disease-free survival for each group. We recorded no interaction between the two hypotheses ($p_{interaction}$=0·886). We also detected no effect of the protocol amendment on treatment efficacy (for monotherapy *vs* sequential treatment $p_{interaction}$=0·390, for UFT *vs* S-1 $p_{interaction}$=0·781; appendix).

3-year overall survival with monotherapy was 55·8% (95% CI 51·7–59·6) and that with sequential treatment was 59·3% (95% CI 55·3–63·0), with no significant difference between groups (HR 0·93, 95% CI 0·79–1·09, p=0·342). 3-year overall survival with UFT was 54·3% (95% CI 50·3–58·2) and that with S-1 was 60·7% (95% CI 56·7–64·5; HR 0·81, 95% CI 0·69–0·93, p=0·013).

The most common grade 1 or 2 adverse events were anaemia (1102 [77%] of 1433 patients), followed by neutropenia (767 [54%] of 1433), leucopenia (710 [50%] of 1433), anorexia (600 [42%] of 1433), and fatigue (547 [38%] of 1433); which were rarer in the UFT only group than in the other treatment groups (appendix). The most common grade 3–4 haematological adverse event was neutropenia (table 2), whereas leucopenia occurred in less than 7% of patients in each treatment group (table 2). Thrombocytopenia and febrile neutropenia occurred in less than 1% of patients. Grade 3–4 non-haematological adverse events mostly occurred in less than 5% of patients, except for anorexia (table 2). We recorded no unexpected toxic effects and no treatment-related deaths.

Subgroup analyses for disease-free survival showed no interaction between factors used for randomisation and other characteristics in the comparison of monotherapy and sequential treatment or the comparison of UFT and S-1 (appendix). S-1 had a stronger treatment effect in more advanced cases according to cytological staging

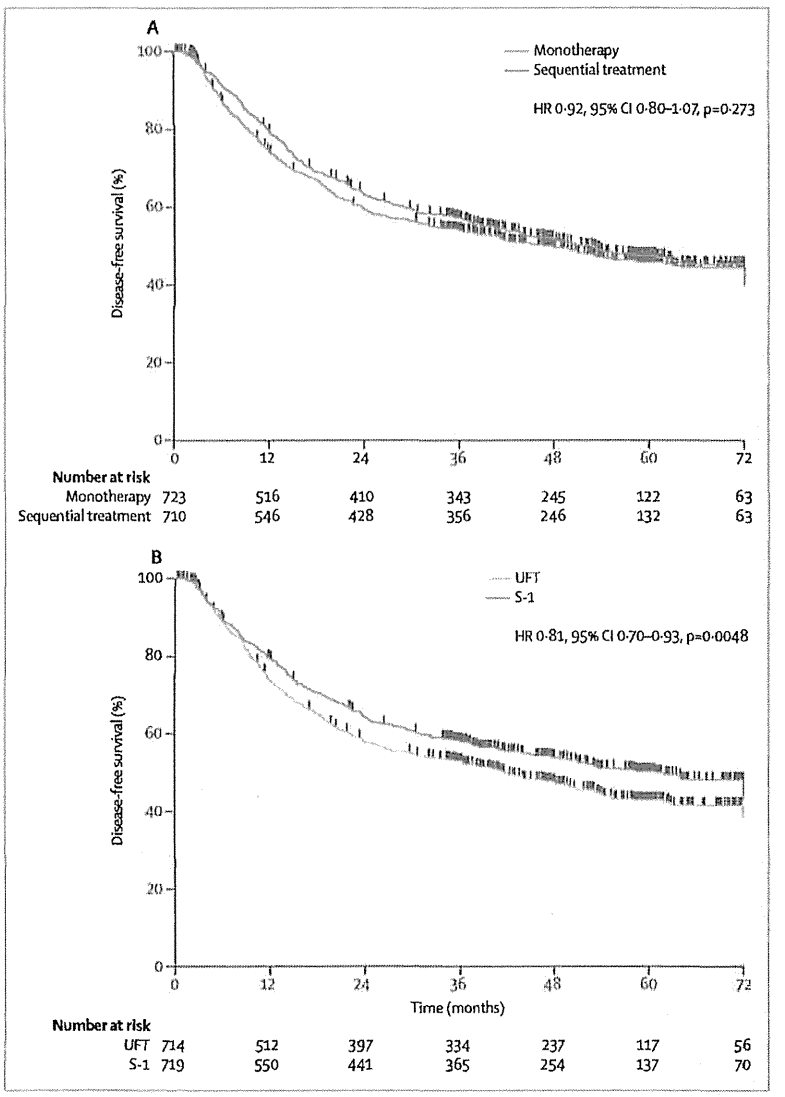

Figure 2: Kaplan-Meier analysis of disease-free survival for UFT versus S-1 (A), and by treatment group (B)

($p_{interaction}$=0·038) and pathological staging, ($p_{interaction}$=0·093). Sequential treatment was better than was monotherapy for patients with stage IIIb disease, but not significantly so. Peritoneal recurrence occurred in 93 (26%) patients taking UFT only, 75 (22%) taking S-1 only, 81 (22%) taking paclitaxel then UFT, and 60 (17%) taking paclitaxel then S-1.

Discussion

Sequential paclitaxel did not improve disease-free survival and UFT was not non-inferior to S-1; S-1 was superior to UFT as adjuvant treatment for T4a or T4b gastric cancer. These results suggest that S-1 monotherapy should remain the standard treatment for locally advanced gastric cancer in Japan.

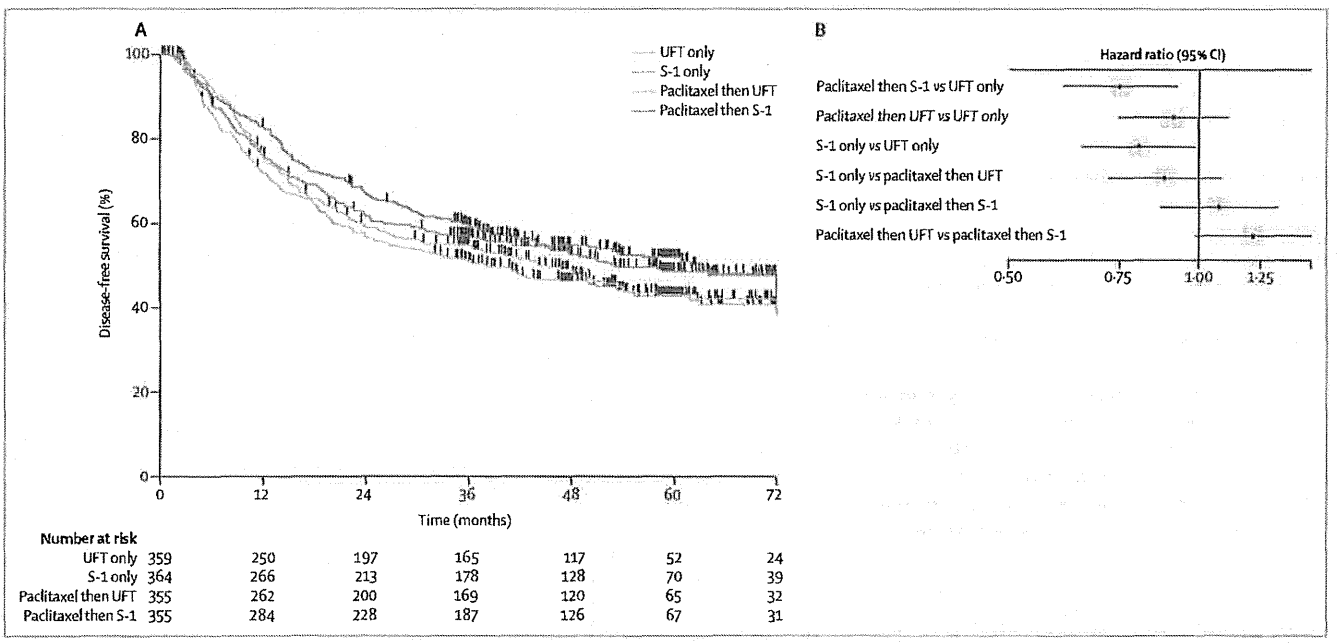

Figure 3: Analysis of overall survival, by Kaplan-Meier (A) and forest plot (B)

	UFT only (n=359)	S-1 only (n=363)	Paclitaxel then UFT (n=355)	Paclitaxel then S-1 (n=356)
Haematological				
Leucopenia	6 (2%)	8 (2%)	22 (6%)	16 (4%)
Neutropenia	41 (11%)	48 (13%)	46 (13%)	83 (23%)
Abnormal platelets	3 (1%)	1 (<1%)	0 (0%)	2 (1%)
Anaemia	1 (<1%)	11 (3%)	3 (1%)	6 (2%)
Non-haematological				
Allergic reaction	0 (0%)	0 (0%)	2 (1%)	3 (1%)
Fever	0 (0%)	1 (<1%)	3 (1%)	3 (1%)
Fatigue	8 (2%)	12 (3%)	11 (3%)	16 (4%)
Anorexia	21 (6%)	24 (7%)	7 (2%)	18 (5%)
Nausea	6 (2%)	7 (2%)	1 (<1%)	4 (1%)
Vomiting	3 (1%)	3 (1%)	1 (<1%)	1 (<1%)
Stomatitis	0 (0%)	2 (1%)	0 (0%)	1 (<1%)
Diarrhoea	4 (1%)	8 (2%)	2 (1%)	11 (3%)
Hypotension	0 (0%)	2 (1%)	1 (<1%)	0 (0%)
Dyspnoea	0 (0%)	1 (<1%)	1 (<1%)	2 (1%)
Motor neuropathy	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Sensory neuropathy	0 (0%)	1 (<1%)	2 (1%)	1 (<1%)
Abnormal total bilirubin	8 (2%)	10 (3%)	2 (1%)	2 (1%)
Abnormal AST concentration	6 (2%)	3 (1%)	8 (2%)	4 (1%)
Abnormal ALT concentration	5 (1%)	3 (1%)	13 (4%)	4 (1%)
Serum creatinine concentration	0 (0%)	2 (1%)	0 (0%)	0 (0%)

Data are n (%). One patients allocated to UFT only was treated with paclitaxel then S-1. Grade 3–4 febrile neutropenia, infection, myalgia, arthralgia, arrhythmia, pigmentation, and albumin decrease occurred in less than 0·5% of patients in each group. AST=asparatate aminotransferase. ALT=alanine aminotransferase.

Table 2: Grade 3 and 4 toxic effects

To our knowledge, the SAMIT trial is the largest-ever adjuvant trial for gastric cancer. Few other large randomised adjuvant trials have been done for gastric cancer, especially after radical lymph node dissection (panel 2). D2 gastrostomy was done for only 10% of patients in the INT 0116 trial[33] and 38% in the MAGIC trial.[2] ACTS-GC,[3] CLASSIC,[4] and ARTIST[34] included patients only after D2 dissection. Adjuvant chemotherapy showed a survival benefit in two of these studies: S-1 in ACTS-GC and capecitabine and oxaliplatin in CLASSIC. Although not the primary analyses, our findings showed the superiority of S-1 compared with UFT. S-1 monotherapy has been considered a robust adjuvant regimen after radical gastrectomy. Patients' characteristics were different in ACTS-GC and SAMIT: about 55% of patients had stage III disease and 0% had stage IV disease in ACTC-GC, compared with 60% and 10% in SAMIT. This difference could explain the difference in survival and compliance between the studies. The subgroup analysis in ACTS-GC suggested that treatment might have less of an effect in patients with stage III disease than in those with stage II disease.[3,35] In SAMIT, we recorded numerically but not statistically improved survival and fewer peritoneal recurrences in patients who received sequential treatment; however, sequential treatment was only effective for patients with stage IIIB disease. A meta-analysis[36] suggests that treatment with several drugs could be more effective than treatment with using fewer (or lower doses), but this finding has not been confirmed in the adjuvant setting.[37]

Weight loss after surgery is an independent risk factor for discontinuation of S-1 adjuvant chemotherapy for

Panel 2: Research in context

Systematic review

We searched Medline, PubMed, and The Cochrane Library with the terms "gastric cancer" (or "stomach cancer"), "adjuvant chemotherapy", and "Japan" for clinical trials published between Jan 1, 1980, and March 31, 2005.[5] We retrieved 12 reports, but only four trials[28–31] met the inclusion and exclusion criteria for our meta-analysis. The eight reports were excluded because they used historical controls, were retrospective studies, control was not surgery alone, or not adjuvant chemotherapy. For the four trials the estimated hazard ratio for surgery plus adjuvant chemotherapy compared with surgery alone for overall survival was 0·73 (95% CI 0·60–0·89, p=0·002). Meta-analysis focused of UFT produced similar results,[32] however, most of the included trials were small and adjuvant chemotherapy was not recognised as a standard treatment. In 2007, the ACTS-GC trial[3] showed the superiority of S-1 compared with surgery alone. S-1 has since become a standard treatment in Japan.

Interpretation

Sequential paclitaxel did not improve disease-free survival and UFT was not non-inferior to S-1, while S-1 was superior to UFT as adjuvant treatment for T4a or T4b gastric cancer. Taken together with ACTS-GC,[3] S-1 monotherapy should be the standard treatment in this setting, at least in Asian populations. Because sequential paclitaxel is safe with good compliance and improves survival, it could be considered for patients with advanced disease.

gastric cancer.[20] In patients with inssuficient oral intake, gastrointestinal adverse events (eg, anorexia, nausea, and vomiting) can cause major distress; such events were less frequent in the sequential groups in SAMIT. In a randomised controlled trial[10] for metastatic breast cancer, the incidence of grade 3–4 nausea, vomiting, or diarrhoea was 3·2% for patients given paclitaxel and 14·0% for those given docetaxel. 10–50% of patients have morbidity after surgery[38] and post-gastrectomy disturbances for 3 months,[39,40] therefore a low toxicity, albeit less effective, regimen is preferable for this initial period. In general practice, the number of elderly patients with cancer who have more comorbidities is increasing;[41] such patients are under-represented in clinical trials.[42] Taxane-containing adjuvant chemotherapy is feasible for older patients with breast cancer and toxic effects can be reduced by sequential treatment regimens.[43]

Our study has some limitations. Staging for randomisation was intraoperative and lavage cytology was not mandatory, but this approach was taken for practical reasons; also, an early and adequate clinical decision to start adjuvant treatment would benefit both patients and clinicians. We used disease-free survival as the primary endpoint because it enabled us to assess the data sooner than if we had used overall survival, although overall survival is the gold standard endpoint for trials of adjuvant treatment for gastric cancer. Nevertheless, the GASTRIC group has said[44] that disease-free survival is an acceptable surrogate for overall survival in trials of cytotoxic drugs for gastric cancer in the adjuvant setting, which suggests that any observed benefit for disease-free survival could translate into a benefit for overall survival in the future.

Contributors

AT, KY, YM, KO, SM, MB, and JS formed the coordinating committee, designed, developed, and revised the protocol, analysed and interpreted data, and prepared the report. KO and MB did statistical analyses. All other authors collected data, and reviewed and helped to revise the report.

Declaration of interests

KY has received honoraria from Taiho, Pfizer, Chugai, Kyowa Hakko, and Yakult, and is a consultant or advisor for Taiho and Hoffman La Roche. RF has received personal fees from Medicon, and grants from Otsuka and Ajinomoto. SM has received personal fees from Bristol and Taiho. NT has received honoraria from Taiho, Chugai, and Pfizer. MB is a shareholder of International Drug Development Institute. The other authors declare no competing interests.

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Diagnostic value of infrared (IR) thermography for assessing diabetic foot in a dialysis patient - A case report

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SUMMARY

Diabetic foot ulcers (DFUs) are a common complication in patients with diabetes mellitus. Highly sensitive medical devices for diagnosing DFUs may therefore be helpful in clinical practice. We investigated whether Infrared (IR) thermography was useful for evaluating the efficacy of treatment in maintenance hemodialysis (MHD) patients with DFUs. IR thermography was used to assess the change in skin temperature during a hemodialysis session. Data on temperature were obtained from six different points on the soles of both feet of an 86-year-old man. We aimed to evaluate whether a polyacrylonitrile (PAN) dialysis membrane had merit as a treatment option in this patient.

As expected, the skin temperature of the sole of the foot increased significantly during the 4-hour dialysis session (0 min vs. 15 min, 27.0 ± 1.9 vs. 28.0 ± 1.6, p= 0.004; 0 min vs. 240 minutes, 27.0 ± 1.9 vs. 33.0 ± 0.4, p= 0.0004). The time series of thermographical images were also consistent with these statistical data.

We concluded that IR thermography may be useful for diagnosing and selecting suitable dialysis conditions for patients with DFUs. The measurements were non-invasive and to not harm our patients.

KEY WORDS: Diagnostic value, IR thermography, diabetic foot ulcers, dialysis patients.

DER DIAGNOSTISCHE WERT DER INFRAROTTHERMOGRAPHIE IN DER BEURTEILUNG DES DIABETISCHEN FUßES BEI EINEM DIALYSEPATIENTEN- EIN FALLBERICHT

Ulzerationen des diabetischen Fußes (DFUs) sind häufige Komplikationen von Patienten mit Diabetes mellitus. Hochempfindliche Medizingeräte für die Diagnose von DFUs könnten deshalb in der klinischen Praxis hilfreich sein. Wir untersuchten, ob die Wirksamkeit der Therapie bei chronischen Dialyse-Patienten mit DFUs mit Infrarotthermographie erhoben werden kann. Die Veränderung der Hauttemperatur während einer Hämodialyse-Behandlung wurde mittels Infrarotthermographie aufgezeichnet. Temperaturewerte wurden an sechs Punkten an den Fußsohlen eines 86 Jahre alten Manns gemessen. Ziel der Untersuchung war es zu klären, ob ein Polyacrylonitrile-Dialyse-Membran(PAN) ein vorteilhafte Therapieoption für diesen Patienten darstellt.

Wie erwartet, erhöhte sich die Hauttemperatur der Fußsohlen während der 4 Stunden dauernden Dialyse signifikant (0 min vs. 15 min, 27.0 ± 1.9 vs. 28.0 ± 1.6, p= 0.004; 0 min vs. 240 min, 27.0 ± 1.9 vs. 33.0 ± 0.4, p= 0.0004). Die Serie der Wärmebilder, die während dieses Zeitraum aufgenommen worden waren, stimmten mit den statistischen Daten überein.

Wir schließen, dass der Einsatz der Infrarotthermographie für die Diagnose und Auswahl von geeigneten Dialysebedingungen von Patients with DFUs hilfreich sein kann. Die Messungen sind nicht-invasiv und belästigen die Patienten nicht.

SCHLÜSSELWÖRTER: Diagnostischer Wert, Infrarotthermographie, diabetischer Fuß, Dialyse-Patient.

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Introduction

Approximately, 300,000 patients currently receive dialysis treatment in Japan[1], with the cause of renal failure in nearly 40% of these patients being diabetic nephropathy. It is therefore an urgent issue for health care providers to improve clinical practice and prevent progression of this disease in Japan[2].

Dialysis patients with diabetes mellitus commonly have complications, such as retinopathy and neuropathy. Diabetic foot ulcers (DFUs) are also a serious comorbidity[3]. It is well documented that DFUs contribute to increased mortality in these patients [4], and therefore need to be treated adequately. We recognized that a number of our dialysis patients with DFUs suffered from coldness, numbness, or pain in their feet. Although we observed that these symptoms were clearly associated with the severity of the DFUs, it proved considerably more difficult to provide suitable therapy against immeasurable subjective symptoms. In other words, we currently do not have sufficient clinical evidence for reducing the risk of DFUs such as recommended skin temperature. Therefore, quantitative analysis of a symptom such as coldness could be helpful for physicians to consider better management of DFUs.

To date, infrared (IR) thermography has become available as a medical procedure in hospitals[5]. It is a non-contact and non-invasive measurement that maps the surface temperature of an object in a remote manner. Medical IR thermography is used currently to study blood flow, detect breast cancer, and evaluate the diabetic foot[6,7]. In this

study we attempted to measure the skin temperature of a dialysis patient's feet during a dialysis session by using IR thermography to evaluate whether dialysis conditions had an impact on skin temperature. The aim of this investigation was to investigate whether IR thermography had diagnostic value in the field of dialysis therapy. The following is a case report to evaluate this possibility.

Methods

We investigated an 86-year-old patient with DFUs who had received hemodialysis for approximately 10 years. Prior to the start of this study, the dialysis membrane was changed from polysulfone to polyacrylonitrile (PAN) after informed consent was obtained from the patient. We used a PAN/AN69 membrane, H 12 (Gambro, Japan). We speculated that the PAN/AN69 membrane could contribute to better management of the DFUs in this patient. The detailed reason for this possibility is reviewed in the "Discussion" section. We assessed whether our therapeutic strategy was effective and selected a reliable method such as IR- thermography to evaluate treatment. We considered that IR-thermo graphy would be suitable for our patient because it is a non-invasive procedure.

We used a medical thermography system named Infra-Eye 3000 (Nihon Kohden Co. Ltd, Japan; Fujitu Tokki System Ltd, Japan), which is used in hospitals in Japan. Skin temperature was calculated simultaneously using the computer software in that system.

The measurement conditions were as follows: room temperature approximately 25° C, acetate-free citrate dialysate (Carbostar®, Ajinomoto Pharmaceuticals Co. Ltd., Japan), dialysate temperature 36.0°C, dialysate flow 500 mL/min, and blood flow rate 200 mL/min. The body temperature of the patient ranged between 35.5 to 36.5°C. Electric carpet with a temperature of approximately 30°C was placed under the patient's legs.

The distance from the patient's foot to the thermography unit was 60 cm. The temperature was measured at six different points of the soles of both feet during the 4 hour hemodialysis session. Detailed information of the measurement points is described in Figure 1. We compated the mean temperature at the measurement points at 0, 15, 30, 60, 180, and 240 minutes during the dialysis session. The series of measurements were repeated three times. With the exception of the patient's body temperature the conditions of the experiment were fixed during the observations.

Representative data of the measurements are shown in the Results section. Statistical analysis was performed using Stat View software version 5.0 for Windows. One-way ANOVA was used to evaluate the change in surface skin temperature of the patient. The data were expressed as mean ± standard deviation, with $P < 0.05$ considered statistically significant.

Results

Pictures of the patient's feet are shown in Figure 1. We detected a slight worsening in skin color of the tiptoe in both feet and a skin ulcer in the right leg. These findings indicated that the patient had a diabetic foot ulcer. We also noticed that the skin temperature was markedly lower on palpation. The thermography results are shown in Figure 2, with the photographs arranged in chronological order from A to F (A start of dialysis session, B 15 min, C 30 min, D 60 min, E 180 min, and F 240 min at end of the session). The letters and squares in each picture represent points where temperature was measured repeatedly. We were also able to detect a higher temperature zone in the area adjacent to the electronic carpet. Figure 3 shows the foot sole temperatures of a healthy middle-aged man. Comparison of this photo with photo A in Figure 2 shows that skin temperature was lower in the patient.

Statistical analysis of the changes in mean temperature at the six measuring points showed the temperature increased gradually from the centre to the periphery in both feet (Figs 2, 4). The improvement in skin surface temperature during the dialysis sessions was statistically significant ($P < 0.0001$).

Clinical monitoring showed the number of skin ulcers in the patient's feet reduced after the dialysis membrane was changed as described in the Methods section. We also found that subjective symptoms of the patients such as coldness, pain, fatigue, and skin conditions in the feet improved following the change in dialysis membrane.

Discussion

Several reports have been published on the diagnostic value of IR thermography in the diabetic foot and neuropathy [5-8]. In contrast, there has been only limited research on the efficacy of IR thermography as a clinical procedure in dialysis patients [9]. In this case study we showed that IR thermography was useful for assessing improvements in skin temperature gradients during a dialysis session.

As far as we are aware, this is the first study of its kind and the results are novel.

Our results raise two major clinical points. First, foot sole skin temperature in dialysis patients with DFUs may be considerably lower than normal (Figure 2). Because it is likely the DFUs will be worsened by this condition, physicians should be encouraged to pay greater attention to improving foot temperature in daily clinical practice. Second, the skin temperature of both feet improved significantly in our patient during dialysis therapy. This finding indicates further research is warranted on whether dialysis conditions such as choice of dialysis membrane, dialysate type and temperature, duration of dialysis session, and rate of blood flow may affect the peripheral circulation in dialysis patients. Several studies have reported that cytokines such as interleukin-1 (IL-1), IL-2, and tumor necrosis factor (TNF) are produced in the peripheral blood of maintenance hemodialysis patients[10-12]. This immunological response may be caused by contact between the blood and dialysate or dialysis membrane. The amount of these cytokines produced may be influenced by factors such as the dialysate condition, endotoxin contamination, and membrane structure. As desctibed in the Methods section, we selected a PAN/AN69 membrane with the aim of improving management of DFUs in this patient[13,14]. According to previous research, generation of bradykinin (BK) was detected with this membrane[15]. It is also well known

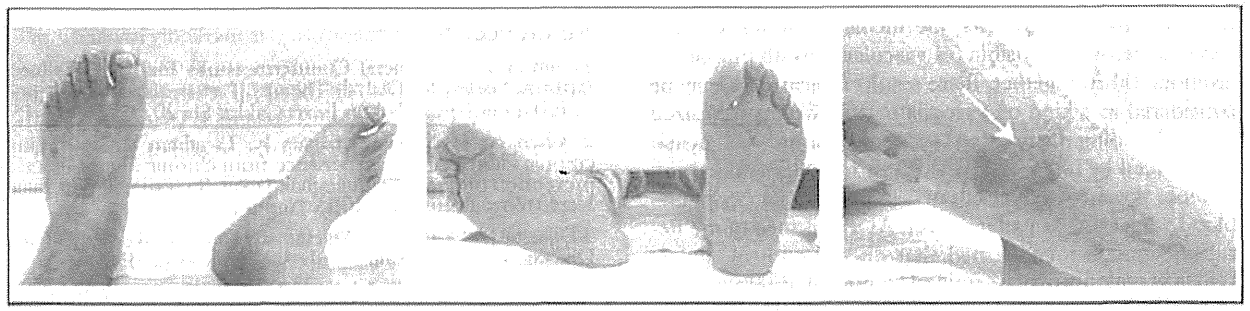

Figure 1.
Photos of the patient's feet. We observed that the skin color of both tiptoes was slightly worsened.
The arrow in the right panel shows a diabetic foot ulcer.

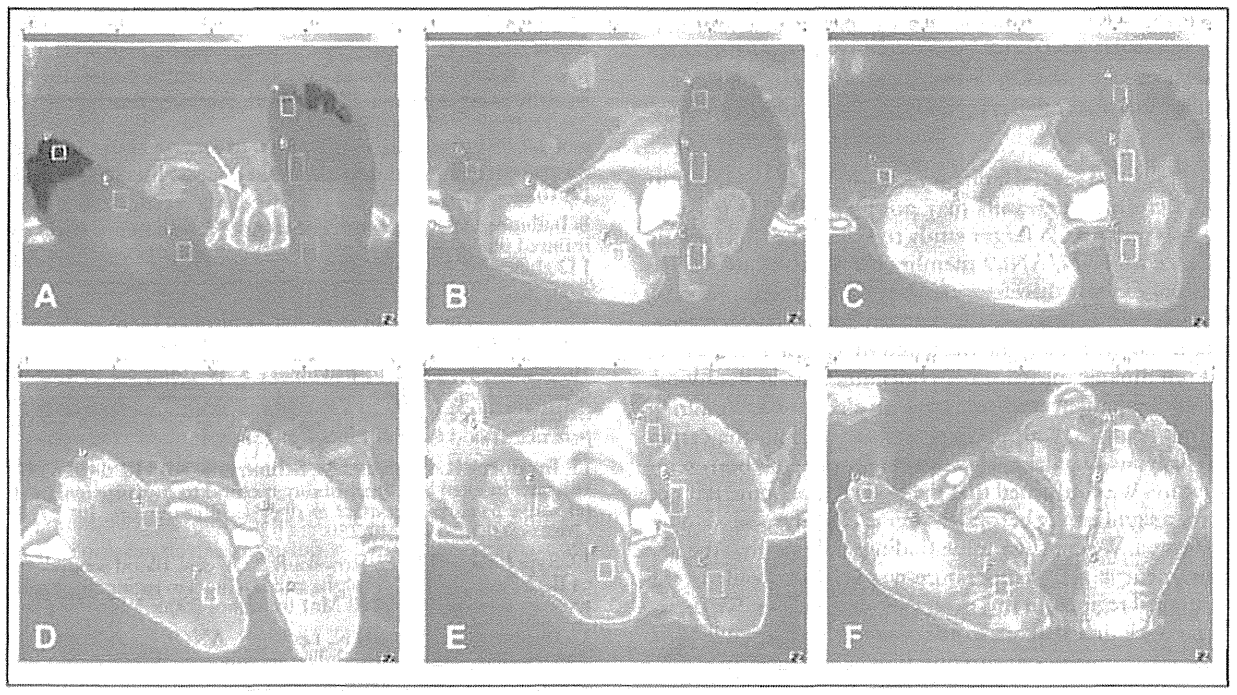

Figure 2.
The results of IR thermography arranged in chronological order.
Photo A was obtained at the start of the dialysis session (0 min), B at 15 min, C at 30 min, D at 60 min, E at 180 min, and F at the end of therapy (240 min). The letters and squares shown in each panel represent the points where skin temperature was measured and calculated (A to C were on the left foot sole and D to F were on the right foot).

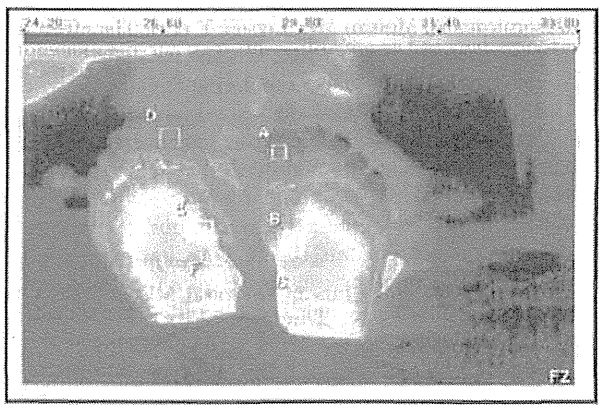

Figure 3.
This image was a obtained from a heathy volunteer and was used as reference data in the study.

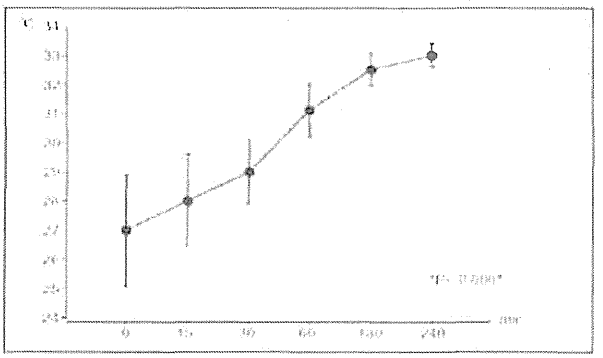

Figure. 4.
The increase in foot sole skin temperature during the dialysis session. The data shown are representative of three independent observations.
The error bars represent the standard deviation of mean temperature of the six measurement points shown in Figure 2 (A to F).

that the effect of BK may be mediated by nitric oxide (NO), a factor responsible for vascular smooth muscle relaxation. Taken together, these results indicate BK may be considered as a kind of vasodilator[15]. We hypothesized that our finding of increased skin temperatures was possibly induced by improved blood flow in peripheral tissues, or more precisely, as a result of vasodilation of peripheral blood vessels in the patient's feet. As mentioned in the Results section, we confirmed that disease control against DFUs in patients may be refined by careful observation of the patient's symptoms for several months. Taken together, our results suggest that the PAN/AN69 membrane has advantages in the treatment of DFUs in dialysis patients. While it is necessary to consider the adverse effects of using PAN/AN69 membranes such as allergic reactions during hemodialysis [16,17], our case report suggests these membranes may also have beneficial effects [13]. This possibility is worth considering and warrants further investigation.

Our study had several limitations. First, it was a case report and therefore the results may not be applicable to other dialysis patients. A larger study to assess the therapeutic efficacy of PAN/AN69 membranes with the aid of IR-thermography is therefore necessary in the future. Second, although we postulated that the increase in skin temperature in the feet might be mediated by BK production, we did not directly measure BK concentrations in the blood. Third, the patient routinely used an electric carpet during dialysis sessions, with the temperature of both the carpet and dialysate maintained lower than the patient's body temperature. We confirmed that the body temperature did not change significantly before or after each dialysis session investigated. We consider these findings indicate that the improvement in skin temperature was mediated only in the peripheral regions, in this case, the patient's feet. We therefore concluded that we could exclude the possibility of these characteristics improving foot skin temperature.

In conclusion, although our study had several limitations, we demonstrated that IR thermography had diagnostic value and could provide important clinical information in dialysis patients with DFUs. Although there are no established criteria for skin temperature levels to determine the pathophysiology of DFUs, we consider that quantitative analysis of skin temperature of dialysis patients' feet using IR thermography adds new insights on clinical guidelines such as " adequate or recommended management of foot skin temperature for dialysis patients with DFUs". Accumulation of knowledge and experience of the IR thermography test will also contribute to refining clinical practice in the field of dialysis therapy.

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The authors have no relevant financial interests to declare.

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Matched Pair Analysis to Examine the Effects of a Planned Preoperative Exercise Program in Early Gastric Cancer Patients with Metabolic Syndrome to Reduce Operative Risk: The Adjuvant Exercise for General Elective Surgery (AEGES) Study Group

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ABSTRACT

Background. Because obesity is a risk factor during surgery, the effects of a preoperative exercise program to reduce the incidence of peri- and postoperative complications in patients with a high body mass index (>25 kg/m^2) and metabolic syndrome were investigated. An assessment of the effects of prospectively planned preoperative exercise was performed in a prospective matching study comparing an exercise testing group and a usual preoperative preparation group who underwent gastrectomy for gastric cancer in Japan.

Methods. Stage I gastric cancer patients with metabolic syndrome diagnosed according to the criteria of the Japanese Ministry of Health, Labor, and Welfare underwent surgery after preoperative exercise. The control group was selected from a database using an individual matching approach for surgery, sex, weight, body mass index, volume of visceral fat, and institution. The primary end point was the frequency of postoperative complications such as cardiovascular events, pneumonia, and surgery-related abdominal complications.

Results. Data from a total of 72 patients (54 in the surgery-alone group, 18 in the preoperative exercise group) were analyzed. The median operative time and amount of bleeding were 208 min and 130 ml in the surgery-alone group and 248 min and 105 ml in the exercise group, respectively. Postoperative complications occurred in one case (5.5 %) in the exercise group and 22 (40.7 %) cases in the surgery-alone group.

Conclusions. Preoperative exercise is safe, and its benefits in reducing postoperative complications are promising and therefore warrant further investigation.

Several clinical studies have demonstrated that obesity is a substantial risk factor for surgery. Obesity is often associated with various pre- and postoperative complications, such as cardiovascular, pulmonary, and metabolic disorders, that can lead to increased postoperative morbidity.

Body mass index (BMI) is a widely accepted indicator of obesity that is easily calculated from the height and weight of an individual. A higher BMI is related to longer operative times, increased intraoperative bleeding, and decreased number of dissected lymph nodes.[1,2] In addition, patients with a higher BMI exhibit higher rates of postoperative complications, such as surgical site infection, anastomotic leakage, abdominal abscesses, and pneumonia.[3–7] However, the relationship between BMI and long-term outcomes after surgery for cancer remains controversial and has not been fully elucidated to date.[8,9]

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With regard to obesity and surgical complications, other studies have investigated the significance of individual fat areas in various obese patients.[10] The results suggest that the accumulation of excess visceral fat is significantly correlated with intra-abdominal infection, postoperative mortality, and longer hospital stays, as well as the incidence of pancreatic fistulas after total gastrectomy.[10,11]

On the basis of this background, we postulated that a preoperative effort to minimize the risk of obesity might alleviate symptoms and decrease the frequency of postoperative complications. We thus searched for the best method to treat preoperative obesity in a relatively short period of time. Although diet therapy and/or exercise are the most common methods of long-term control, the use of diet restriction before surgery may risk the physical condition of the patient. Therefore, on the basis of a report showing that the amount of visceral fat can be reduced by exercise without diet control, we adopted preoperative exercise as a specific intervention.[12–14] In this prospective study, we evaluated whether preoperative exercise in early gastric cancer patients with obesity and metabolic syndrome is effective and safe for reducing the incidence of postoperative complications compared with that observed in a matched control group.

PATIENTS AND METHODS

Study Population

Consecutive stage I gastric cancer patients (clinical T1N0/T1N1/T2N0) with metabolic syndrome undergoing open or laparoscopic, distal or total gastrectomy with D1+ to D2 lymph node dissection between February 2007 and January 2013 at the Kanagawa Cancer Center and Asa Municipal Hospital were enrolled in the exercise group.

The definition of metabolic syndrome complied with the criteria determined by the Japanese Ministry of Health, Labor, and Welfare. Briefly, the following criteria were used: male: height of $\geq$160 cm and waist circumference of $\geq$85 cm; and female or male: height of <160 cm and a waist circumference of $\geq$80 cm, with more than 1 of the following: (1) Triglyceride $\geq$ 150 mg/dl and/or high density lipoprotein cholesterol <40 mg/dl; (2) systolic blood pressure $\geq$130 mm Hg and/or diastolic blood pressure $\geq$85 mm Hg; (3) Fasting blood sugar $\geq$ 110 mg/dl. (The use of medications for hyperlipidemia, hypertension, or diabetes mellitus [DM] was regarded as having each item irrespective of the laboratory data.) The other inclusion and exclusion criteria have been previously described.[14]

In order to complete the exercise program, the patients were required to be able to walk >200 m on a flat floor and climb two consecutive stairs without rest. In addition, the patients were required to exhibit no ischemic changes on a treadmill ECG within 6 weeks before registration.

Each patient in the exercise group was individually matched with three control patients on the basis of the approach of surgery, sex, weight, BMI ($\pm$2), volume of visceral fat, and institution. The control patients were sampled from the Kanagawa Gastric Database, a large concurrent cohort.

Interventions

The patients enrolled in the exercise group were required to have started the following protocol treatment within 14 days of registration.

The training program was composed of three components: aerobic exercise, resistance training, and stretching. The primary training was aerobic exercise, such as the use of a treadmill or bicycle ergometer, swimming, dancing, or jogging. The aerobic training was performed 3–7 days per week. The strength of the training was set according to the maximal heart rate reserve (Karvonen method) or the Borg scale to rate the level of perceived exertion.[15,16] The expected energy expenditure of exercise was 30 kcal/kg/wk. Resistance training was carried out once or twice per week. Stretching was performed before and after the aerobic training. The total energy expenditure was measured using a calorie counter (Lifecorder, Suzuken, Japan).

Gastrectomy was performed within 7 days after completing 4 weeks of the protocol exercise.

Follow-Up

Physical, complete blood count, and blood biochemistry examinations were scheduled weekly to monthly until 1 month after finishing the protocol. A follow-up survey to assess the postoperative status and survival was completed 1 year after the operation.

Outcomes

The primary outcome was the proportion of postoperative complications. The operative time, amount of intraoperative bleeding, and number of hospital days were compared between the exercise and control groups. The changes in the volume of visceral fat and body weight from baseline before and after the program were measured in the exercise group to evaluate the direct effects of the exercise.

Analysis Methods

Regarding the baseline characteristics, the means and proportions were compared by the *t* test or Wilcoxon

signed-rank test and Chi squared test. The changes in the indices in the exercise group were summarized and assessed by the paired *t*-test and Wilcoxon sign test.

In comparisons between groups, the odds ratios (ORs) and 95 % confidence intervals (95 % CIs) were estimated, and statistical tests were conducted by logistic regression analysis. The Kaplan-Meier method and the log-rank test were used to estimate the rate of discharge and compare the arms with regard to the length of hospital stay.

The study protocol was registered with the UMIN Clinical Trial Registry (UMIN-CTR) on February 7, 2007 (http://www.umin.ac.jp/ctr/index-j.htm).

RESULTS

Eighteen patients were enrolled in the exercise group, and 54 control group patients receiving conventional standard preoperative care were matched to the exercise group patients.

Patient Characteristics

The baseline characteristics of the patients in the exercise and control groups are shown in Table 1. The age, sex, BMI, and performance status of the two groups were similar. For body composition, significant differences between the two groups were detected concerning the visceral fat area estimated on computed tomographic scan images.

There were no differences in terms of the operative procedures, such as the surgical approach (open or laparoscopic), type of gastrectomy (distal or total), and reconstruction method (Billroth I or Roux-en-Y). There were also no differences regarding the extent of gastric cancer, i.e., the pathological depth of invasion, lymph node metastasis, and stage of the disease, between the two groups. A total of 100 % (18 of 18) of the patients in the exercise group and 96.3 % (52 of 54) of the patients in the control group had either stage IA or IB gastric cancer.

TABLE 1 Patient characteristics

Characteristic	Exercise ($n = 18$)	Control ($n = 54$)	p value
Age (years)	63.1 (51–76)	66.1 (39–81)	0.230
Sex (male)	18 (100.0 %)	51 (94.4 %)	0.307
BMI (kg/m^2)	26.7 (23.1–31.2)	25.6 (20.8–34.1)	0.151
ECOG performance status 0	18 (100 %)	54 (100 %)	1.000
Waist circumference (cm)	95.8 (81–112)	92.2 (80–115)	0.072
Subcutaneous fat area (cm^2)	161.5 (69–260)	152.6 (76.3–314.9)	0.473
Visceral fat area (cm^2)	221.9 (95.8–375.7)	180.8 (65.1–363.9)	0.023
Medical treatment for			
Hypertension	7 (38.8 %)	21 (38.9 %)	1.000
Hyperlipidemia	6 (33.3 %)	7 (13.0 %)	0.052
Diabetes mellitus	2 (11.1 %)	6 (11.1 %)	1.000
Operative procedure			
Approach			
Open	9 (50.0 %)	26 (48.2 %)	0.892
Laparoscopic assisted	9 (50.0 %)	28 (51.9 %)	
Gastrectomy			
Distal	14 (77.8 %)	40 (74.1 %)	0.753
Total	4 (22.2 %)	14 (25.9 %)	
Reconstruction			
Roux-en-Y	8 (44.4 %)	26 (48.2 %)	0.785
Billroth I	10 (55.6 %)	28 (51.8 %)	
Lymph node dissection			
D1+	17 (94.4 %)	41 (76.0 %)	0.086
D2	1 (5.6 %)	13 (24.0 %)	
No. of collected lymph nodes	40.3 (16–103)	43.7 (9–104)	0.560
Combined resection	2 (11.1 %)	2 (3.7 %)	0.235
Pathological tumor stage (JCGC, 13th ed.)			
T			
T1 (m/sm)	9/9 (100 %)	16/27 (79.6 %)	0.26
T2 (mp/ss)	0/0 (0 %)	5/4 (16.7 %)	
T3 (se)	0 (0 %)	2 (3.7 %)	
N			
N0	16 (88.9 %)	46 (85.2 %)	0.709
N1 (perigastric)	2 (11.1 %)	6 (11.1 %)	
N2 (regional)	0 (0 %)	2 (3.7 %)	
Stage—IA	16 (88.9 %)	47 (87.0 %)	0.698
IB	2 (11.1 %)	5 (9.3 %)	
II	0 (0 %)	0 (0 %)	
IIIA	0 (0 %)	2 (3.7 %)	

BMI body mass index, *ECOG* Eastern Cooperative Oncology Group, *JCGC* Japanese Classification of Gastric Cancer

Effects of Exercise on Various Parameters of Metabolic Disease

After 4 weeks of the preoperative exercise program, the changes in the indices in the exercise group before surgery were evaluated (Table 2). There were no severe exercise-associated adverse events. After the preoperative exercise program, BMI, body weight, and abdominal circumference were significantly decreased. As a consequence, the volume of visceral fat, which is allegedly correlated with perioperative morbidity, was also significantly decreased (Fig. 1), although the decrease in subcutaneous fat was not significant compared to the status observed before the introduction of the exercise program.

Effects on Surgery

There were no notable differences in terms of the operative time and amount of intraoperative bleeding

TABLE 2 Changes in various indices before operation in the exercise group ($n = 18$)

Variable	Mean (95 % CI)	p value for change
Changes in body mass index (kg/m^2)	−0.48 (−0.79 to −0.18)	0.004
Changes in body weight (kg)	−1.34 (−2.19 to −0.49)	0.004
Changes in abdominal circumferences (cm)	−2.28 (−4.27 to −0.28)	0.028
Changes in volume of subcutaneous fat (cm)	−9.3 (−27.6 to 9.1)	0.302
Changes in volume of visceral fat (cm^2)	−34.8 (−64.7 to −4.9)	0.025

CI confidence interval

between the two groups. The median amount of bleeding was slightly lower in the exercise group (median 105 ml, range 10–1,280 ml) than in the control group (median 130 ml, range 0–1,320 ml) (Table 3). In both groups, D1+ lymph node dissection was performed in most cases. D2 lymph node dissection was carried out in one (5.6 %) case in the exercise group and 13 (24.1 %) cases in the control group.

Resection of other organs was conducted in two (11.2 %) cases in the exercise group and two (3.7 %) cases in the control group.

The duration of hospital stay is shown in Fig. 2. The median duration of hospitalization was 9.0 and 10.0 days in the exercise and control groups, respectively (log-rank test, $p = 0.038$). More patients were hospitalized for longer periods in the control group.

Postoperative Complications

The observed postoperative complications are listed in Table 3.

In the exercise group, no complications regarding postoperative bleeding, shock, or thrombosis were observed, whereas two grade 3 events were noted in the control group ($p = 1.000$).

With regard to wound infections, none of the 18 patients in the exercise group exhibited wound infections. However, nine cases (four grade 1 events, three grade 2 events, and two grade 3 events) of wound infections occurred in the control group (OR 0.21, 95 % CI 0.00–1.10, $p = 0.125$).

Concerning respiratory complications, three cases of grade 1 lung atelectasis were observed in the exercise group, while eight cases (seven grade 1 events and one grade 3 event) of atelectasis and two cases (one grade 1 event and one grade 3 event) of pneumonia were reported (OR 1.15, 95 % CI 0.17–5.62, $p = 1.000$).

More serious complications after gastrectomy were also examined. Five cases of grade 2 and four cases of grade 3 anastomotic leakage, eight pancreatic fistulas (two grade 1 events, four grade 2 events, and two grade 3 events), 10 intra-abdominal abscesses, and two severe abdominal complications were observed in the control group. No such complications were observed, except for one grade 2 pancreatic fistula in the exercise group (OR 0.12, 95 % CI 0.00–0.89, $p = 0.033$).

With respect to intra-abdominal abscesses, none was observed in the exercise group; however, three grade 2 and seven grade 3 intra-abdominal abscesses were reported in the control group (OR 0.18, 95 % CI 0.00–0.96, $p = 0.089$).

DISCUSSION

Obesity is one of the most serious public health problems as a result of its metabolic and cardiovascular complications, which negatively affect life expectancy and quality of life. Although the incidence of obesity and metabolic syndrome has been increasing in the general population of Japan, the precise impact of these disorders

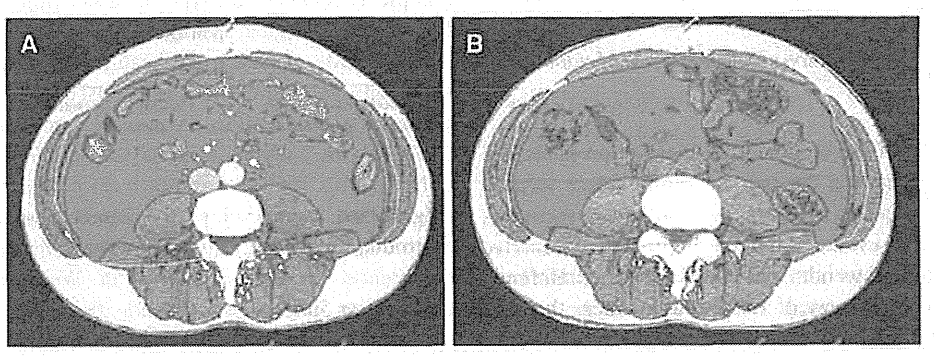

FIG. 1 Comparison between preexercise visceral fat area (VFA) (**a**) and postexercise VFA (**b**) of a patient in the exercise group. The VFA was decreased from 146.65 to 103.52 cm^2

TABLE 3 Surgical results

Characteristic	Exercise ($n = 18$)	Control ($n = 54$)	OR (95 % CI)	p value
Intraoperative outcome, median (min–max)				
Operation time (min)	248 (140–443)	208 (120–398)		0.185
Estimated blood loss (ml)	105 (10–1280)	130 (0–1320)		0.692
Postoperative complications				
Nonsurgical				
Respiratory				
All grades	3	8	1.15 (0.17–5.62)	1.000
Grade 2 or more	0	1	–	
Surgical				
Extra-abdominal				
Wound infection				
All grades	0	9	0.21 (0–1.10)	0.125
Grade 2 or more	0	5	0.42 (0–2.44)	0.452
Intra-abdominal				
Abdominal abscess				
All grades	0	10	0.18 (0.00–0.96)	0.089
Grade 2 or more	0	10	0.18 (0.00–0.96)	0.089
Anastomotic leakage				
All grades	0	9	0.21 (0.00–1.10)	0.125
Grade 2 or more	0	9	0.21 (0.00–1.10)	0.125
Pancreatic fistula				
All grades	1	8	0.34 (0.01–2.89)	0.565
Grade 2 or more	1	6	0.48 (0.01–4.37)	0.872
Bleeding				
All grades	0	2	1.23 (0–10.53)	1.000
Grade 2 or more	0	2	1.23 (0–10.53)	1.000
Other				
All grades	0	2	1.23 (0–10.53)	1.000
Grade 2 or more	0	1	–	
Total (intra-abdominal)				
All grades	1	18	0.12 (0.00–0.89)	0.033
Grade 2 or more	1	15	0.16 (0.00–1.18)	0.086
Total (wound infection + intra-abdominal)				
All grades	1	22	0.09 (0.00–0.64)	0.008
Grade 2 or more	1	16	0.14 (0.00–1.07)	0.063

OR odds ratio, *CI* confidence interval

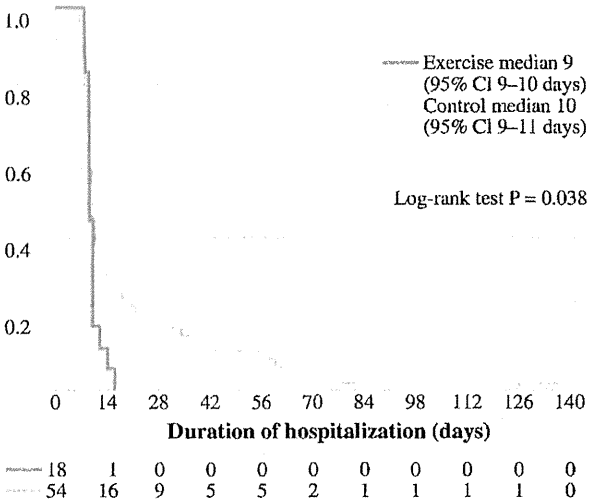

FIG. 2 Duration of hospital stay

on surgical outcomes has not been clarified to date. BMI is widely used as an indicator of obesity and can be easily calculated using a patient's height and weight. The World Health Organization has suggested the use of the BMI cutoff point of >25 kg/m^2 to designate obesity, which is additionally subdivided into three subcategories, including overweight (25–29.9 kg/m^2), obese (30–39.9 kg/m^2), and very obese (>40 kg/m^2).

The relationships between BMI and early and late surgical outcomes after gastrectomy for gastric cancer have been documented in several retrospective studies.[4–6] However, the influence of an overweight status on surgical outcomes, i.e., the quality and extent of surgery, incidence of postoperative complications, length of hospital stay, and prognosis after gastric cancer surgery, remains controversial. Furthermore, the degree of intra-abdominal fat accumulation is assumed to increase the technical difficulty of performing abdominal surgery even though the level of BMI does not always coincide with the degree of visceral fat accumulation. The amount of visceral fat in this respect is another independent substantial risk factor for perisurgical problems in patients undergoing abdominal surgery.

The present study focused on the risk factors for postoperative complications after gastrectomy with curative intent in Japan. In Japan, gastrectomy with extended systematic lymphadenectomy (D2 dissection) has long been the standard surgical treatment, even for early, superficial cancers. This approach has resulted in superior stage-by-stage survival compared to that observed in most Western countries and has led to a complete cure in a proportion of patients with nodal disease beyond the perigastric region, although this finding has not been confirmed in Western randomized trials owing to an increase in postoperative morbidity and mortality.[17,18] The significantly higher prevalence of obese patients in Western countries is claimed to be the reason for the discrepant findings observed between the East and West.

In this regard, we first planned a prospective randomized phase II clinical trial comparing a group that participated in a

preoperative exercise program to a group that received conventional, standard preoperative care.[14] However, after interviewing eligible patients to obtain informed consent for the trial, we realized the difficulty in persuading overweight patients with metabolic dysfunction to participate in the study, especially enrolling in the control group. Therefore, we ultimately decided to implement a prospective 1:3 case-matching study comparing a preoperative exercise program group to a conventional preoperative care group.

Because we exclusively confined the study to patients who were eligible for Asian-style gastrectomy for early, superficial gastric cancer, the differences in technical problems were controlled between the two groups. We also adjusted the backgrounds of the patients by five factors: age, sex, number of factors regulating metabolic syndrome, institution, and preexisting cardiovascular/respiratory risks.

Two important findings were obtained from the present study. The obvious effects of our preoperative exercise program on overweight patients with metabolic dysfunction were demonstrated. The risk factors in terms of BMI, abdominal circumference, and number of factors for metabolic syndrome were significantly improved by our preplanned, relatively short-term preoperative exercise program. The other unexpected favorable finding was a significant decrease in visceral fat. Such a reduction in intra-abdominal fat facilitates delicate surgical procedures, such as D2 lymphadenectomy for gastric cancer.

As for the operative time and amount of blood loss during surgery, there were no significant differences between the exercise and control groups.

The rate of postoperative complications was improved in the exercise group compared to the control group. The incidence of postoperative cardiovascular and respiratory problems was decreased by the exercise program, as was that of surgical site infections. The incidence of other serious postoperative problems, such as anastomotic and/or pancreatic duct leakage and intra-abdominal abscess formation, also significantly decreased in the exercise group.

In conclusion, the present study found that a preoperative exercise program significantly improved operative risk factors and decreased the frequency of serious postoperative complications that are common in patients who are overweight and who have metabolic syndrome. Further prospective studies are needed to clarify the precise effects of preoperative exercise programs in other gastric cancer populations in which different comorbidities exist.

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DISCLOSURE The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis

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Abstract

Background Hangeshashinto (TJ-14, a Kampo medicine), which reduces the level of prostaglandin E2 and affects the cyclooxygenase activity, alleviates chemotherapy-induced oral mucositis (COM). We conducted a randomized comparative trial to investigate whether TJ-14 prevents and controls COM in patients with gastric cancer.

Methods We randomly assigned patients with gastric cancer who developed moderate-to-severe oral mucositis (CTCAE v4.0 grade ≧1) during any cycle of chemotherapy to receive either TJ-14 or a placebo as a double-blind trial. The patients received a placebo or TJ-14 for 2–6 weeks according to the chemotherapy regimen from the beginning of the next course of chemotherapy. The primary end point was the incidence of grade ≧2 oral mucositis in the protocol treatment course, and the secondary end points were the time to disappearance of oral mucositis and the incidence of adverse events.

Results Following the key opening of the blinding protocol, we analyzed 91 eligible patients (TJ-14: 45, placebo: 46) using a "per protocol set" analysis. The incidence of ≧grade 2 COM was 40.0 % in the TJ-14 group and 41.3 % in the placebo group ($p = 0.588$). The median duration of ≧grade 2 COM was 14 days in the TJ-14 group and 16 days in the placebo group ($p = 0.894$). Meanwhile, the median duration of any grade of COM was 9 days in the TJ-14 group and 17 days in the placebo group among the patients who developed grade 1 symptoms during the screening cycle [hazard ratio 0.60; 95 % CI (0.23–1.59), $p = 0.290$].

Conclusions Although TJ-14 treatment did not reduce the incidence of ≥2 COM in the patients who developed mucositis during chemotherapy for gastric cancer, a trend was observed in which TJ-14 reduced the risk of COM in the patients who developed grade 1 COM during the screening cycle. Further, phase III studies with a larger sample size are needed to clarify the protective effects of TJ-14 for COM.

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Keywords Oral mucositis · Hangeshashinto (TJ-14) · Chemotherapy · Gastric cancer

Introduction

Gastric cancer is the second most frequent cancer-related cause of death after lung cancer [1]. Chemotherapy is one of the most important modalities for treating advanced gastric cancer as well as curatively resected cancers in the adjuvant setting. Numerous chemotherapy regimens have been used in cases of operable or inoperable gastric cancer [2–5]. Although several studies have shown that chemotherapy improves and prolongs survival, it often causes severe toxicity, seriously compromising the patient's quality of life and precluding the continuation of the treatment.

Oral mucositis is a common toxicity associated with cytotoxic chemotherapy used in the gastric cancer treatment. In pivotal phase III trials of chemotherapy for gastric cancer, the incidence of all grades of chemotherapy-induced oral mucositis (COM) was observed to be 6.3–32 % [4–8]. COM results in severe discomfort, impairing the patient's ability to eat, swallow, and talk, and has an indirect effect on tumor outcomes, as its presence often necessitates the unfavorable modification of anticancer therapy, such as breaks in the administration of chemotherapy or dose reduction in the chemotherapy regimen [9–11]. One factor associated with COM exacerbation is the activation of the cyclooxygenase pathway, which mediates ulcer formation and pain via the upregulation of pro-inflammatory prostaglandins. Indeed, Richard et al. demonstrated, after having enlisted 20 patients treated with chemotherapy drugs and performing a biopsy of the oral mucosa in each case, a statistically significant increase in the number of endothelial cells in the oral mucosa with nuclear factor-kappa B (NF-κB) and cyclooxygenase 2 (COX-2) expressions in the postchemotherapy treatment period compared to that observed in the pretreatment period. The expression of COX-2 in these cells represents the initial sign of the inflammatory cascade that determines the production of prostaglandins and further tissue damage. COX-2 is also upregulated by NF-κB, which plays an important role in the inflammatory process [12]. COM invariably requires treatment with systemic analgesics, adjunctive medications, physical therapy, and psychological therapy in addition to oral care [13]. Treatment guidelines developed by the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology have been published; however, they also highlighted the need for a higher level of evidence [14]. Although a range of interventions have been developed to prevent and treat COM, a more rational approach is warranted [11].

Hangeshashinto (TJ-14) is a traditional Japanese medicine containing 7 herbal crude drugs. Seven herbal crude drugs are as follows; Pinelliae tuber, Scutellariae Radix, Glycyrrhizae Radix, Zizyphi Fructus, Ginseng Radix, Zingiberis Processum rhizoma, and Coptidis rhizome [15–17]. TJ-14 is prescribed in Japan to treat inflammatory diarrhea, gastritis, and stomatitis. Recently, Kono et al. [18] found that TJ-14 was effective as a gargle therapy for the treatment of COM in a pilot clinical study and a randomized, placebo-controlled clinical trial. TJ-14 has been demonstrated to directly inhibit PGE2 production in human gingival fibroblasts and reduce the PGE2 content in the colon in several animal models of diarrhea using anticancer drugs, cholera toxin, or castor oil, resulting in the amelioration of inflammatory damage [19–22]. It has also been reported that some ingredients of TJ-14 inhibit PGE2 production and/or the COX-2 expression [23–32]. Phenylpropanoids, such as [6]-shogaol and [6]-gingerol, flavonoids, such as wogonin, baicalein, and baicalin, and isoquinoline alkaloids, such as berberine, are well established to possess an anti-PGE2 activity via various particular mechanisms.

Considering these clinical and biochemical study findings, in the present study, the efficacy of TJ-14 in the prevention and/or treatment of COM was investigated in a randomized, double-blind, placebo-controlled clinical trial of patients receiving chemotherapy for gastric cancer.

Materials and methods

Study design

A prospective, multi-institutional, randomized, double-blind, placebo-controlled phase II trial was performed in patients receiving chemotherapy for gastric cancer in Japan. Patients who developed CTCAE v4.0 ≧grade 1 oral mucositis during the screening cycle of chemotherapy were considered eligible for inclusion in this study. The eligible patients were centrally randomized to receive either TJ-14 or a placebo during their next cycle of chemotherapy. The patients were stratified according to age, chemotherapy regimen, institution, and previous treatment for oral mucositis before randomization in a 1:1 ratio. A specially made and prepared matched placebo was utilized to confirm blinding.

The primary objective of this study was to determine the efficacy and safety of TJ-14 compared with the placebo. The primary end point was the incidence of ≥grade 2 oral mucositis, and the worst oral mucositis grade observed throughout the protocol therapy was assessed. As for severity, the worst grade observed on the day of the medication was evaluated instead of the mean circadian change. The secondary end points were the time to disappearance of oral mucositis and the incidence of adverse events.