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進行胃癌に対するD3郭清の意義：胃癌
大動脈周囲リンパ節画像診断転移陽性
例におけるD3郭清術の意義と問題点
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機
胃癌腹膜播種制御を目的とした多機能分子生物学的治療の開発
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H．知的財産権の出願・登録状況

1．特許取得
特記なし

2．実用新案登録
特記なし

3．その他
特記なし

別紙４

研究成果の刊行に関する一覧

辻仲利政

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Subcuticular sutures versus staples for skin closure after open gastrointestinal surgery: a phase 3, multicentre, open-label, randomised controlled trial

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Summary

Background Staples have been widely used for skin closure after open gastrointestinal surgery. The potential advantages of subcuticular sutures compared with staples have not been assessed. We assessed the differences in the frequency of wound complications, including superficial incisional surgical site infection and hypertrophic scar formation, depending on whether subcuticular sutures or staples are used.

Methods We did a multicentre, open-label, randomised controlled trial at 24 institutions between June 1, 2009, and Feb 28, 2012. Eligible patients aged 20 years or older, with adequate organ function and undergoing elective open upper or lower gastrointestinal surgery, were randomly assigned preoperatively to either staples or subcuticular sutures for skin closure. Randomisation was done via a computer-generated permuted-block sequence, and was stratified by institution, sex, and type of surgery (ie, upper or lower gastrointestinal surgery). Our primary endpoint was the incidence of wound complications within 30 days of surgery. Analysis was done by intention to treat. This study is registered with UMIN-CTR, UMIN000002480.

Findings 1080 patients were enrolled and randomly assigned in a one to one ratio: 562 to subcuticular sutures and 518 to staples. 1072 were eligible for the primary endpoint and 1058 for the secondary endpoint. Of the 558 patients who received subcuticular sutures, 382 underwent upper gastrointestinal surgery and 176 underwent lower gastrointestinal surgery. Wound complications occurred in 47 of 558 patients (8·4%, 95% CI 6·3–11·0). Of the 514 who received staples, 413 underwent upper gastrointestinal surgery and 101 underwent lower gastrointestinal surgery. Wound complications occurred in 59 of 514 (11·5%, 95% CI 8·9–14·6). Overall, the rate of wound complications did not differ significantly between the subcuticular sutures and staples groups (odds ratio 0·709, 95% CI 0·474–1·062; p=0·12).

Interpretation The efficacy of subcuticular sutures was not validated as an improvement over a standard procedure for skin closure to reduce the incidence of wound complications after open gastrointestinal surgery.

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See Comment page 1076

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Introduction

Wound complications are among the most common issues reported after surgery, and are often very problematic for patients in terms of cosmetic appearance, decreased quality of life, prolonged hospital stays, and increased health-care costs.[1,2] Several publications have addressed ways to reduce the risk of wound complications associated with surgery,[3–6] such as intraoperative administration of antimicrobial prophylaxis,[4,5] skin preparation, barrier retractional wound protection,[7] use of absorbable sutures during intraperitoneal procedures,[8,9] and pulsatile lavage irrigation of wounds before closure.[10,11] Triclosan-coated sutures significantly reduced the rate of surgical site infections compared with conventional uncoated sutures in various types of surgery.[12]

Because of the increase in the number of patients with preoperative comorbidities that are risk factors for wound complications, such as malnutrition,[13] diabetes mellitus,[14] and obesity,[15] new, innovative approaches will be necessary to decrease the risk of wound complications after surgery. Subcuticular suturing for skin closure is an attractive alternative for skin approximation in most types of surgery. It is often used in plastic surgery because of the low incidence of wound complications and good cosmetic appearance.[16–18] Compared with staples, several clinical trials have shown that subcuticular sutures are associated with a significantly lower incidence of wound complications and better cosmetic results after orthopaedic surgery,[19] cardiovascular surgery,[20,21] and caesarean section.[22,23]

In 242 patients undergoing coronary artery bypass graft surgery, Johnson and colleagues[24] prospectively closed half of each sternal and saphenous vein harvest wound with staples and half with intradermal sutures. The incidence of wound infection was similar with both methods, but significantly fewer wound complications were noted with subcuticular sutures than with staples. Additionally, patients who expressed a preference preferred sutures to staples. Basha and investigators[25] randomly assigned 435 patients undergoing caesarean delivery to stainless steel staples or subcuticular 4-0 monocryl sutures. They

reported that staple closure was associated with a four-times increased risk of wound separation (adjusted odds ratio [OR] 4·66, 95% CI 2·07–10·52; p<0·001) and poor patient satisfaction.

These trials had been done for class 1 surgical procedures—ie, clean surgery. However, the benefit of subcuticular sutures in gastrointestinal surgery, a class 2 (clean-contaminated) surgery that is associated with a high incidence of wound complications,[15,26,27] has not been fully examined.[28] Staples are the most commonly used technique for skin closure during gastrointestinal surgery because of convenience and speed. Because no consensus has been reached about how to apply findings from class 1 surgery to class 2 surgery, an optimum method of skin for gastrointestinal surgery remains to be established.

We investigated differences in prevention of wound complications between subcuticular sutures and staples after elective upper and lower gastrointestinal open surgery.

Methods

Study design and participants

We did a large-scale, multicentre, open-label, phase 3 randomised controlled trial at 24 institutions in Japan from June 1, 2009, to Feb 28, 2012. The study was organised by the Clinical Study Group of Osaka University on Risk Management (OSGO-RM), which is composed of hospitals affiliated from the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University.

Eligible patients were undergoing elective upper or lower gastrointestinal surgery, aged 20 years or older, and had adequate organ function. Patients undergoing abdominoperineal resection for rectal cancer were also eligible, but we only assessed abdominal wounds for outcomes. We excluded patients needing emergency or laparoscopic surgery, with a history of laparotomy with a midline incision, or with long-term corticosteroid use; active infection such as peritonitis, pneumonia, or urinary tract infection; massive ascites; coagulopathy or other disorders that would preclude study participation; uncontrolled or insulin-treated diabetes; mental illness, poor general condition; severe cardiopulmonary disease; or who were deemed by surgeons to be inappropriate for participation in a randomised trial. The institutional review board of each hospital approved the protocol. All patients provided written informed consent before randomisation. We did not collect data on the number of patients approached and assessed for eligibility.

Randomisation and masking

Patients were recruited by the investigators and treatment allocation was made preoperatively after confirming eligibity.

Enrolment was done through a web-based system established for this trial and randomisation by a computer-generated permuted-block sequence. The size of the blocks used for randomisation was four. Patients were randomly assigned (1:1) to either subcuticular sutures or staples for skin closure and balanced according to institution, sex, and type of surgery (ie, upper or lower gastrointestinal open surgery). Investigator surgeons were informed of the treatment allocation via the internet and did the procedures. Patients and investigators were not masked to group assignment. The data centre, based at the Multicenter Clinical Study Group at Osaka University was responsible for treatment allocation, central monitoring, and statistical analyses under the supervision of the statistician in charge.

Procedures

In the subcuticular suture group, surgeons used interrupted subcuticular sutures with 3-0 or 4-0 monofilament absorbable suture (polydioxanone; PDS-II Ethicon, Tokyo, Japan). The interval of the sucuticular sutures was 15–25 mm and the length of the bite of sutures was 15–25 mm from the edge of the skin. Under this condition, the skin could be closed tightly. Use of sterile strips or skin glue for epidermal approximation in addition to subcuticular sutures was an institutional choice. In the staples group, metallic skin staples, which were the choice of individual institutions, 10–15 mm apart were used. Approximation of the fat layer was not allowed in the either group. Before the trial, investigators from participating institutions were instructed on how to do subcuticular sutures during the trial. A video in which a plastic surgeon used the subcuticular suturing technique (adopted as the standard) was provided to each participating institution. The standard procedure was also demonstrated at each investigator meeting. Investigators and physicians in training met yearly to examine how subcuticular sutures were done.

All participating institutions were asked to follow the guidelines about prevention of surgical site infections issued by the US Centers for Disease Control and Prevention (CDC).[29] Surgical gloves and instruments were changed before wound closure. Absorbable monofilament sutures were used for approximation of the fascia, and the subcutaneous space was irrigated with saline without added antibiotics. Intra-abdominal drain placement through a separate incision away from the operative incision was permitted but drainage of the wound was not allowed. Skin preparation techniques, prophylactic antibiotic administration, the volume of saline used for intra-abdominal irrigation, dressing methods, and timing of postoperative staple removal, perioperative care, and wound management were according to each participating institution's respective standards.

Our primary outcome was incidence of wound complications within 30 days of surgery. The secondary outcome was the incidence of hypertrophic scar formation 6 months after surgery. Wound complications were defined as the presence of at least one of several signs or symptoms necessitating treatment: wound disruption,

stitch abscess, abscess caused by metal allergy, seroma or haematoma, or superficial incisional surgical site infections. Superficial incisional surgical site infections are defined by the CDC[29] as infections occurring within 30 days of surgery that implicate only the skin or subcutaneous tissue of the incision. Diagnosis of superficial incisional surgical site infection must satisfy one or more of several criteria: purulent drainage (with or without laboratory confirmation) from the superficial incision, organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision, or at least one of the signs or symptoms of infection (pain or tenderness, localised swelling, redness or heat, and superficial incision deliberately opened by the surgeon, unless the incision is culture-negative). Infection control personnel monitored and detected surgical site infections during patients' hospital stays. Changes noted in the wound were not defined as wound complications if they did not necessitate treatment. When superficial incisional surgical site infections and other wound complications coexisted in the same patient, we defined the complication as superficial incisional surgical site infections. We defined hypertrophic scar as a widened or elevated unsightly scar with erythema or pigmentation.

Responsible surgeons checked for the presence or absence of wound complications every day during the hospital stay and at every outpatient visit until 30 days after surgery. They were also responsible for checking for the presence or absence of hypertrophic scar formation at 6 months after surgery, and measured the width and length of detected hypertrophic scars. Before starting the trial, the principal investigator showed typical cases of various wound complications and hypertrophic scars, and consensus about all types of wound complications was reached by the investigators.

Statistical analysis

We planned a sample size of 530 patients per treatment group when we designed the trial. Such a sample size would provide power of 80% with a two-sided significance level of 0·05 to detect superiority in the reduction of the frequency of wound complications. Wound complications were anticipated in 11% of patients in the staples group and 6% in the subcuticular sutures group, allowing for a loss to follow-up of roughly 10%. The projected accrual period was 2 years and no interim analyses were planned.

We did the analysis on a modified intention-to-treat basis. We expressed continuous numerical data as medians and IQRs or means and SDs, when appropriate, and distribution of dichotomous data in percentages with 95% CIs. We used Fisher's exact test to compare binary variables and the Mann-Whitney *U* test to compare continuous variables. All p values of less than 0·05 were deemed significant.

The primary outcome was analysed with Fisher's exact test, and we used the Mantel-Haenszel test to adjust for the type of surgery, a potential confounding factor, which was not prespecified in the protocol. We used Fisher's exact test to analyse the secondary outcome and to calculate and compare outcomes as a post-hoc analysis on the basis of type of surgery.

We analysed thickness of subcutaneous fat (objectively classified by the surgeon as either thin, normal, or thick), American Society of Anesthesiologists (ASA) physical status classification,[30] operative time, intraoperative blood loss volume, duration of prophylactic antibiotics, presence of drainage tube and duration of drainage, and use of postoperative anticoagulant therapy as variables. Subgroups were analysed with logistic regression to assess for statistical interactions between treatments in various subgroups. Because of the exploratory nature of subgroup comparisons, we report test results without multiplicity adjustments for type I error. This study is registered with UMIN-CTR, UMIN000002480. UMIN-CTR is one of the network members of the Japan Primary Registries Network, which meets WHO registry criteria.

Role of the funding source

The sponsor had no roles in the study design; data collection, analysis, or interpretation; or writing of the Article. The corresponding author had full access to all

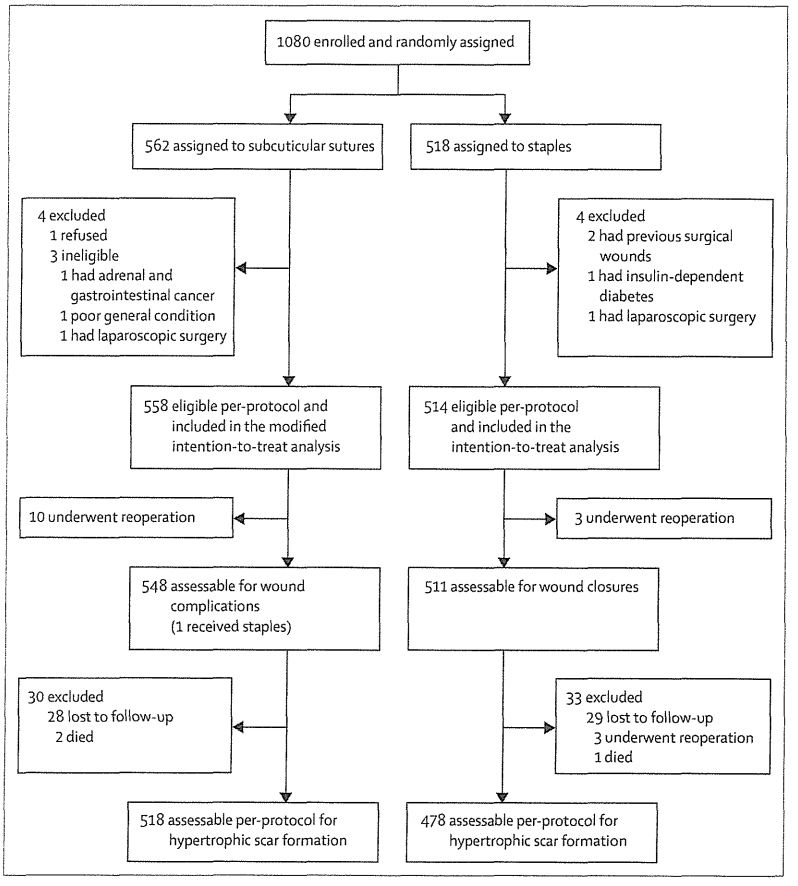

Figure 1: **Trial profile**

	Subcuticular sutures (n=562)	Staples (n=518)
Age (years)	68 (61–75)	68 (61–74)
Sex		
Male	388 (69·0%)	365 (70·5%)
Female	174 (31·0%)	153 (29·5%)
Surgery		
Upper gastrointestinal	385 (68·5%)	417 (80·5%)
Lower gastrointestinal	177 (31·5%)	101 (19·5%)
Thickness of subcutaneous fat*		
Thick	143 (25·6%)	109 (21·2%)
Standard	328 (58·8%)	317 (61·6%)
Thin	87 (15·6%)	89 (17·3%)
ASA physical status classification*		
1	201 (36·0%)	201 (39·0%)
2	313 (56·1%)	273 (53·0%)
3	44 (7·9%)	41 (8·0%)
Operative time (min)*	228 (180–270)	218 (175–264)
Blood loss (mL)	230 (100–430)	244 (120–450)
Wound protection†		
Surgical drape	535 (95·9%)	497 (96·3%)
Gauze	10 (1·8%)	6 (1·2%)
None	13 (2·3%)	13 (2·5%)
Duration of antibiotic prophylaxis (days)*		
1	379 (67·9%)	373 (72·4%)
2	33 (5·9%)	22 (4·3%)
3	100 (17·9%)	86 (16·7%)
≥4	46 (8·2%)	34 (6·6%)
Duration of drain insertion (days)*		
0 (ie, no drain)	118 (21·1%)	108 (21·0%)
1–3	50 (9·0%)	34 (6·6%)
≥4	390 (69·9%)	373 (72·4%)
Duration of hospital stay after surgery (days)	14 (11–21)	15 (12–21)
Anticoagulation therapy‡		
Yes	130 (23·3%)	96 (18·6%)
No	429 (76·7%)	420 (81·4%)

Data are n (%) or median (IQR). ASA=American Society of Anesthesiologists.[30] *Data missing for four patients in the subcuticular sutures group and three patients in the staples group. †Data missing for four patients in the subcuticular sutures group and two patients in the staples group. ‡Data missing for three patients in the subcuticular sutures group and two patients in the staples group.

Table 1: **Baseline demographic and clinical characteristics**

	Subcuticular sutures (n=385)	Staples (n=417)
Diseases		
Gastric cancer	375 (97·4%)	403 (96·6%)
Gastric submucosal tumour	6 (1·6%)	9 (2·2%)
Other	4 (1·0%)	5 (1·2%)
Procedures		
Total gastrectomy	149 (38·7%)	143 (34·3%)
Distal gastrectomy	186 (48·3%)	219 (52·5%)
Proximal gastrectomy	19 (4·9%)	16 (3·8%)
Exploratory laparotomy	4 (1·0%)	4 (1·0%)
Other	27 (7·0%)	35 (8·4%)

Data are n (%).

Table 2: **Types of diseases and surgical procedures in patients undergoing upper gastrointestinal surgery**

	Subcuticular sutures (n=177)	Staples (n=101)
Diseases		
Colon cancer	98 (55·4%)	51 (50·5%)
Rectal cancer	71 (40·1%)	48 (47·5%)
Anal cancer	2 (1·1%)	1 (1·0%)
Other	6 (3·4%)	1 (1·0%)
Procedures		
Right hemicolectomy	41 (23·2%)	28 (27·7%)
Left hemicolectomy	44 (24·9%)	8 (7·9%)
Low anterior resection	61 (34·5%)	38 (37·6%)
Abdominoperineal resection	11 (6·2%)	10 (9·9%)
Partial resection of colon	9 (5·1%)	10 (9·9%)
Other	11 (6·2%)	7 (6·9%)

Data are n (%).

Table 3: **Types of diseases and surgical procedures in patients undergoing lower gastrointestinal surgery**

the data and was responsible for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1080 patients from 24 institutions were enrolled and randomly assigned—562 to subcuticular sutures and 518 to staples. Assessment of case report forms showed that four patients in each group were ineligible for inclusion, and thus the modified intention-to-treat population comprised 558 patients in the subcuticular sutures group and 514 in the staples group (figure 1). Ten patients in the subcuticular sutures group and three in the staples group needed reoperation within 30 days, which met the exclusion criterion, a history of laparotomy, and thus were not assessed for wound complications.

Distribution of most demographic and clinical characteristics of enrolled patients was balanced between groups except type of surgery (table 1). Tables 2 and 3 show details of the diseases and surgical procedures in the two groups. 417 patients who underwent upper gastrointestinal surgery were allocated to the staples group and 385 to the subcuticular sutures group, and 177 patients who underwent lower gastrointestinal surgery were allocated to the subcuticular sutures group and 101 to the staples group.

In the subcuticular sutures group, wound complications occurred in 47 of 558 (8·4%, 95% CI 6·3–11·0) patients, including 36 (6·4%, 4·6–8·8) patients with superficial incisional surgical site infections. In the staples group, wound complications occurred in 59 of 514 patients

	All patients				Upper gastrointestinal surgery				Lower gastrointestinal surgery			
	Subcuticular suture (n=558)	Staples (n=514)	Odds ratio (95% CI)	p	Subcuticular sutures (n=382)	Staples (n=413)	Odds ratio (95% CI)	p	Subcuticular sutures (n=176)	Staples (n=101)	Odds ratio (95% CI)	p
Primary outcome												
Wound complication rate*	47 (8·4%)	59 (11·5%)	0·709 (0·474–1·062)	0·12	29 (7·6%)	39 (9·4%)	0·788 (0·459–1·339)	0·38	18 (10·2%)	20 (19·8%)	0·463 (0·217–0·978)	0·0301
Component outcomes												
Surgical site infection (superficial incisional)	36 (6·4%)	36 (7·0%)	0·928 (0·558–1·543)	0·81	23 (6·0%)	20 (4·8%)	1·259 (0·649–2·461)	0·53	13 (7·4%)	16 (15·8%)	0·425 (0·179–0·992)	0·0399
Non-surgical-site infection	11 (2·0%)	23 (4·5%)	0·435 (0·189–0·940)	0·0238	6 (1·6%)	19 (4·6%)	0·331 (0·107–0·875)	0·0149	5 (2·8%)	4 (4·0%)	0·710 (0·149–3·666)	0·73
Wound separation	3 (0·5%)	8 (1·6%)	0·346 (0·059–1·453)	0·13	1 (0·3%)	6 (1·5%)	0·178 (0·004–1·480)	0·13	2 (1·1%)	2 (2·0%)	0·570 (0·041–7·979)	0·62
Seroma	5 (0·9%)	12 (2·3%)	0·383 (0·105–1·179)	0·09	3 (0·8%)	11 (2·7%)	0·290 (0·052–1·108)	0·06	2 (1·1%)	1 (1·0%)	1·149 (0·059–68·457)	1·00
Haematoma	1 (0·2%)	2 (0·4%)	0·466 (0·008–8·969)	0·61	0 (0·0%)	1 (0·2%)	..	..	1 (0·6%)	1 (1·0%)	0·573 (0·007–45·300)	1·00
Other	2 (0·4%)	1 (0·2%)	1·867 (0·097–110·358)	1·00	2 (0·5%)	1 (0·2%)	2·166 (0·112–128·141)	0·61	0 (0·0%)	0 (0·0%)	..	..

Significance was calculated with Fisher's exact test. *Adjusted odds ratio 0·658 (95% CI 0·438–0·988; p=0·0438 [calculated with Mantel-Haenszel test]).

Table 4: **Primary outcome and its components in modified intention-to-treat population**

(11·5%, 8·9–14·6), including 36 (7·0%, 5·0–9·6) with superficial incisional surgical site infections (table 4). As a primary outcome, the number of wound complications did not differ significantly between the two groups (OR 0·709, 95% CI 0·474–1·062; p=0·12). Since we identified confounding with the stratified factor, type of surgery, adjustment was done to show a significant difference (0·658, 0·438–0·988; p=0·0438), although this was not prespecified.

Post-hoc exploratory analyses showed that wound complications excepting surgical site infections occurred significantly less often in the subcuticular suture group than in the staples group overall (OR 0·435, 95% CI 0·189–0·940; p=0·0238) and in patients who underwent upper gastrointestinal surgery (0·331, 0·107–0·875; p=0·0149). In patients who underwent lower gastrointestinal surgery, significantly fewer wound complications (0·463, 0·217–0·978; p=0·0301) and superficial incisional surgical site infections (0·425, 0·179–0·992; p=0·0399) were noted in the subcuticular sutures than in the staples group (table 4).

Table 5 summarises secondary outcomes. Significantly fewer hypertrophic scars formed in the subcuticular sutures group than in the staples group overall (OR 0·726, 0·528–0·998; p=0·0429) and specifically in patients who underwent upper gastrointestinal surgery (0·672, 0·465–0·965; 0·0282).

We did a post-hoc subset analysis to identify potential interactions between wound complications and background factors (figure 2). Significant risk reduction for wound complications was noted with subcuticular sutures compared with staples in male patients (*vs* female patients), lower gastrointestinal surgery (*vs* upper gastrointestinal surgery), cases with operative time of 220 min or greater (*vs* those with operative times <220 min), and patients receiving postoperative anticoagulant therapy (*vs* those not receiving such therapy). We did not identify any important treatment-related adverse events for stapling or subcuticular sutures.

	n	Hypertrophic scar formation	Odds ratio (95% CI)	p
All patients			0·726 (0·528–0·998)	0·0429
Subcuticular sutures	558	93 (16·7%)		
Staples	514	111 (21·6%)		
Upper gastrointestinal surgery			0·672 (0·465–0·965)	0·0282
Subcuticular sutures	382	66 (17·3%)		
Staples	413	98 (23·7%)		
Lower gastrointestinal surgery			1·226 (0·576–2·729)	0·72
Subcuticular sutures	176	27 (15·3%)		
Staples	101	13 (12·9%)		

Data for hypertrophic scar formation are n (%). Significance was calculated with Fisher's exact test.

Table 5: **Secondary outcomes in the modified intention-to-treat population**

Discussion

Subcuticular sutures for skin closure have been advocated instead of staples in clean (class 1) surgery, including cardiovascular surgery,[24] orthopaedic surgery,[19] and caesarean delivery,[25] on the basis of the results of randomised studies. Whether these results can be applied to class 2 surgery, as represented by gastrointestinal surgery, is of concern. Classification of the types of surgery is described in panel 1. Our results show that subcuticular sutures did not significantly reduce the frequency of

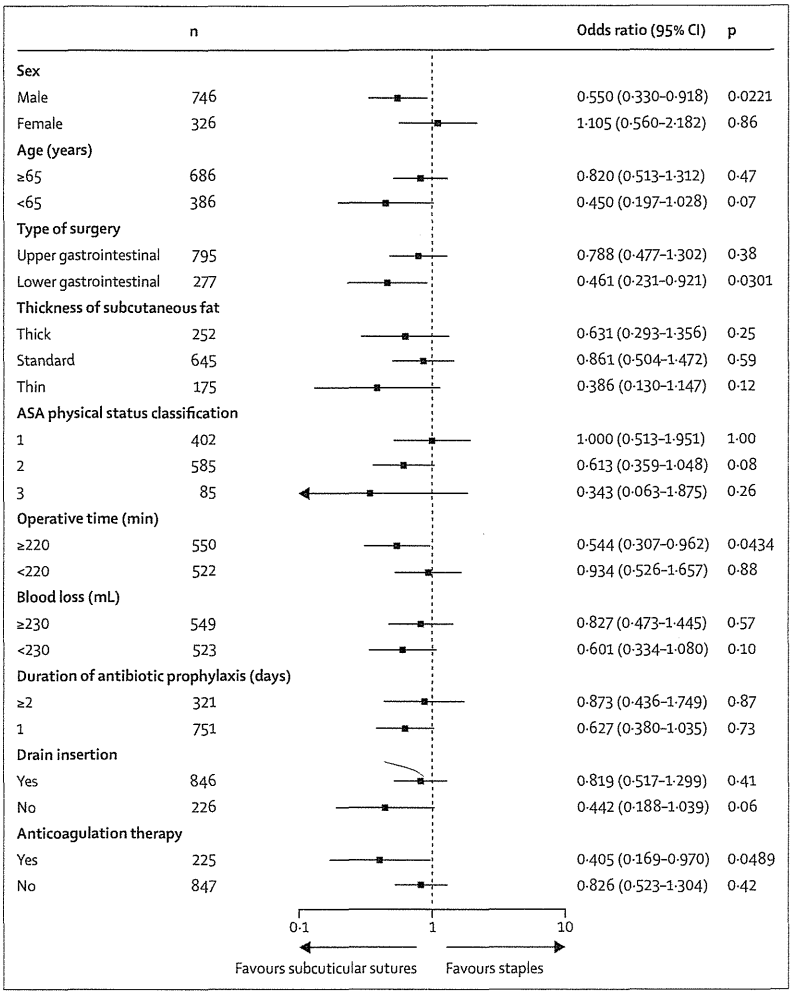

Figure 2: **Subset analysis of wound complications in the modified intention-to-treat population**
Significance was calculated with Fisher's exact test. ASA=American Society of Anesthesiologists.

wound complications as a primary outcome and therefore subcuticular sutures are not validated as a new standard procedure for skin closure after gastrointestinal surgery (panel 2). As a secondary outcome, we noted fewer hypertrophic scars formed when subcuticular sutures were used than when staples were used.

Our sample size calculation was done on the assumption that the incidence of wound complications was 7·5% with upper gastrointestinal surgery and 15% with lower gastrointestinal surgery when staples were used and the expected number of patients receiving the respective surgery was equal (1:1), which gave the incidence of wound complications as 11%. We postulated that a 5% reduction of the incidence of wound complications by subcuticular sutures was necessary to be a new standard procedure for skin closure. There are several reasons why we did not obtain the results we expected. We showed that the incidences of wound complications were 8·4% in the subcuticular sutures group and 11·5% in the staples group (p=0·12) in all patients, 7·6% and 9·4% (p=0·38) in upper gastrointestinal surgery, and 10·2% and 19·8% (p=0·0301) in lower gastrointestinal surgery (table 4). Subcuticular sutures were more effective in lower gastrointestinal surgery, whereas enrolment of patients receiving open lower gastrointestinal surgery was substantially lower than that of patients receiving open upper gastrointestinal surgery (278 *vs* 802) because laparoscopic surgery has become more prevalent in lower gastrointestinal surgery. Although we included type of surgery as one of our stratification variables, more patients who underwent lower gastrointestinal surgery received subcuticular sutures than staples (177 *vs* 101) and more patients who underwent upper gastrointestinal surgery received staples than subcuticular sutures (417 *vs* 385) as a result of the unexpected unbalanced allocation (tables 2, 3), which might be caused by participation of many institutions and the presence of three stratification factors. These factors attenuated the postulated effect of subcuticular sutures and the analysis of the primary outcome did not reach significance. When adjusting for the type of surgery, subcuticular sutures seemed to confer a benefit, although this result is not conclusive. Thus, preferential use of subcuticular sutures might be supported in some circumstances. Although we did not analyse outcomes of individual institutions, there was possibility of heterogeneity with regard to the effect of subcuticular sutures caused by as many as 24 institutions.

Before this trial, few data for potential differences in the rate of wound complications and hypertrophic scar formation between upper and lower gastrointestinal surgery were available. That the incidence of superficial incisional surgical site infections was higher with lower gastrointestinal surgery than with upper gastrointestinal surgery had been previously reported,[15] which was the reason why we used type of surgery as a stratification factor. We showed that the incidence of total wound complications and superficial incisional surgical site infections was significantly higher in lower than in upper gastrointestinal surgery, whereas the incidence of

Panel 1: Classification of types of surgery (class 1 and 2)[29]

Class 1 (clean)
An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. For example, skin procedures (ie, biopsies), simple orthopaedic surgery, vascular surgery, and elective caesarean section.

Class 2 (clean-contaminated)
An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. For example, gastrointestinal surgery, thoracic procedures, gynaecological procedures, and emergency caesarean section.

hypertrophic scar formation was higher in upper than in lower gastrointestinal surgery. Subcuticular sutures reduced the incidence of wound complications compared with staples in lower gastrointestinal surgery and the formation of hypertrophic scars in upper gastrointestinal surgery, possibly because of the higher number of events of those types in these types of surgery, respectively.

Subset analysis showed that subcuticular sutures resulted in significantly fewer wound complications in some subgroups, such as lower gastrointestinal surgery, longer operative time, and postoperative anticoagulant therapy, and the frequency of wound complications in almost all subsets of patients was lower in the subcuticular sutures group than in the staples group.

It is reasonable to employ subcuticular sutures in other types of gastrointestinal surgery, especially hepatobiliary or pancreatic surgery, which exert extensive surgical stress and are associated with large volumes of blood loss, long operative times, and a high incidence of surgical site infections.[41,42] We did not include hepatobiliary or pancreatic surgery in this trial because they contain a wide variety of surgical procedures and different levels of surgical site infection rates. The results of our subset analysis imply that subcuticular sutures could be applied to other types of gastrointestinal surgery and might reduce wound complications.[43]

We persuaded investigators to follow the US national surgical infection prevention guidelines, which recommend that antibiotic prophylaxis should be discontinued within 24 h of surgery.[4] As a result, 67·9% in the subcuticular sutures group and 72·4% in the staples group received prophylaxis with antibiotics for 1 day in this trial. Compared with the result of a national cohort study in the USA,[44] reporting that about 60% of patients who had major surgery were still receiving antimicrobial prophylaxis at 24 h after surgery, our results were acceptable. We did not find an imbalance between the groups.

Our study had several limitations. First, the absence of masking could have biased the detection of wound complications. However, assessment of surgical site infections was done by infection control personnel at the participating institutions who did not have roles in trial design or conduct. Detection of other wound complications was based on whether some treatment (dressing or surgical intervention) for wound management was documented in the medical record, which could minimise bias. However, it was possible that the open nature of our trial might have affected the findings. The Japanese insurance system and common clinical practice permitted examination of patients by responsible surgeons at outpatient clinics 1 month and 6 months after surgery, which allowed for accurate assessment of the wound even though allocation was not masked.

Second, it has been reported that subcuticular sutures for skin closure have advantages compared with staples with regard to cosmetic considerations,[16–18] patient satisfaction,[24,25] and wound handling.[24,25] Nevertheless, we did not assess patients' satisfaction, patients' preference, or potential overall effects on the health-care system, and we did not use a validated scale to assess scars. We did not directly compare costs either, but the price of one stapling device and that of two packs of PDS-II sutures were roughly the same and median operative time was 10 min longer in the subcuticular sutures group (table 1).

In conclusion, the efficacy of subcuticular sutures was not validated as an improvement over a standard procedure for skin closure after gastrointestinal surgery.

Panel 2: Research in context

Systematic review

We searched Medline and the Cochrane Database of Systematic Reviews with the terms "subcuticular suture, cutaneous closure, or dermal closure", "staple or staple closure", and "randomised controlled trial or phase 3 trial". We identified 11 randomised trials: four for caesarean delivery,[25,31–33] three for cardiovascular surgery,[24,34,35] two for orthopaedic surgery,[19,36] one for gynaecological surgery,[41] and one for laparotomy.[28] All these surgical procedures are class 1 (clean) surgery except for laparotomy, for which the details of the specific surgical procedures were not specified in the report. Six trials recommended subcuticular sutures[19,24,25,28,32,34] and four[31,35–37] showed equivalent results for sutures and staples. Only one trial recommended staples.[33] Most were small-scale trials (n=48–435). The number of patients in the trials with equivalent results ranged from 77 to 187. Three[23,38,39] of the four meta-analyses about caesarean delivery recommended subcuticular sutures; the other showed similar outcomes with sutures and staples.[40] A meta-analysis[21] of cardiovascular surgery recommended subcuticular sutures to reduce the number of wound complications. We identified no randomised trials in gastrointestinal surgery.

Interpretation

To our knowledge, our trial is the first done in gastrointestinal surgery (a class 2 surgery). Although the results of most randomised trials done in class 1 surgery support the use of subcuticular sutures to reduce wound complications and improve cosmetic outcomes, the benefits of subcuticular sutures in clean-contaminated surgeries remain unclear. This trial failed to prove subcuticular sutures were a new standard procedure for skin closure after gastrointestinal surgery; however, the formation of hypertrophic scars was significantly reduced with subcuticular sutures compared with staples.

Contributors

TT and KY drafted the paper. TT designed the protocol. YD and MM supervised the design of the trial and assisted with doing the trial. SK and TS obtained and analysed the data. TT, KU, and TI were the main investigators. All other authors participated in study conduct and recruitment of patients.

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Conflicts of interest

We declare that we have no conflicts of interest.

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Clinical Trial Note

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A Phase II Trial of Trastuzumab Combined with Irinotecan in Patients with Advanced HER2-positive Chemo-refractory Gastric Cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group OGSG1203 (HERBIS-5)

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Irinotecan is a key drug in second- or further-line chemotherapy for patients with advanced gastric cancer. Continuous administration of trastuzumab beyond first progression is expected to contribute to the benefit of chemotherapy for human epidermal growth factor receptor 2-positive gastric cancer. The aim of this trial is to evaluate the efficacy and safety of combination chemotherapy with trastuzumab and irinotecan in Japanese patients with advanced human epidermal growth factor receptor 2-positive chemo-refractory gastric cancer. The primary endpoint is the disease control rate. The secondary endpoints are adverse events, overall response rate, time to treatment failure, progression-free survival, overall survival and response rate stratified by prior trastuzumab use. A total of 30 patients will be enrolled in this Osaka Gastrointestinal Cancer Chemotherapy Study Group trial.

Key words: chemo-GI tract HER2-positive – trastuzumab – irinotecan

INTRODUCTION

The worldwide standard of care for first-line treatment of unresectable or recurrent gastric cancer is systemic chemotherapy with platinum and fluoropyrimidine drugs. However, the standard for second-line chemotherapy after failure of the first-line regimen remains to be established. Several Phase III studies have shown a survival benefit with second-line chemotherapy in comparison with best supportive care (1–3). A Japanese trial (WJOG4007) comparing second-line irinotecan (CPT-11) with weekly paclitaxel concluded that neither regimen was superior in terms of efficacy or tolerability (4). One explanation for this may have been the high rate of crossover in subsequent treatment. CPT-11 and taxanes may be also key drugs in second- or further-line chemotherapy for gastric cancer.

Human epidermal growth factor receptor 2 (HER2; also known as ERBB2) is a member of a family of receptors associated with tumor cell proliferation, apoptosis, adhesion, migration and differentiation. HER2 is over-expressed in ~20% of gastric cancer cases (5–7). Trastuzumab, a monoclonal antibody that targets HER2, induces antibody-dependent cellular cytotoxicity, inhibits HER2-mediated

signaling and prevents cleavage of the extracellular domain of HER2. In advanced HER2-positive gastric or gastro-esophageal junction cancer, trastuzumab has shown a survival benefit in first-line combined with standard chemotherapy (8).

Many targeted drugs have shown efficacy of continuation treatment beyond progression (9–11), including bevacizumab in colorectal cancer, rituximab in malignant lymphoma and erlotinib in non-small-cell lung cancer. There is also some evidence to support the benefit of continuing anti-HER2 therapy beyond first progression in HER2-positive metastatic breast cancer (12,13). Therefore, continuous administration of trastuzumab beyond first progression is recommended in clinical practice guidelines on the treatment of breast cancer (14).

Trastuzumab showed at least an additive antitumor effect when combined with CPT-11 in preclinical models of gastric cancer (15). Moreover, the efficacy of FOLFIRI plus trastuzumab has been reported in a retrospective analysis (16). The combination of CPT-11 with trastuzumab showed promising results in the treatment of metastatic breast cancer (17).

Therefore, the goal of this study is to conduct an open-label multicenter Phase II study to evaluate the efficacy and safety of combination therapy with trastuzumab and CPT-11 in refractory gastric cancer.

The Protocol Review Committee of the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) approved the study protocol in July 2012, and the study was initiated in August 2012. This trial was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000008626 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGESTS OF THE STUDY (OGSG1205)

Objective

OGSG1205 is an open-label multicentre Phase II study aimed at evaluating the efficacy and safety of combination therapy with trastuzumab and CPT-11 in patients with advanced HER2-positive chemo-refractory gastric cancer.

Resources

This study is supported by the OGSG.

Endpoints

The primary endpoint of this study is disease control rate (DCR), defined as the proportion of patients showing a complete response, partial response or stable disease as the best overall response according to RECIST. The secondary endpoints are rates of adverse events, overall response rate, time to treatment failure, progression-free survival (PFR), overall survival (OS) and response rate stratified by prior trastuzumab use.

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, patients will be required to fulfill all of the following criteria:

(i) Pathologically confirmed unresectable or recurrent gastric adenocarcinoma or adenocarcinoma of the gastro-esophageal junction.
(ii) HER2-positive confirmed by IHC and/or FISH (IHC 3- or IHC 2- and FISH-positive).
(iii) Disease progression during or after one or more cycles of previous chemotherapy.
(iv) Measurable or nonmeasurable target lesions according to RECIST criteria version 1.1.
(v) Aged $\geq$20 years.
(vi) Performance status (ECOG scale) of 0 or 2.
(vii) Sufficient oral intake.
(viii) Adequate baseline organ and marrow function.
(ix) Life expectancy of $>$3 months.
(x) Left ventricular ejection fraction of $\geq$50%.
(xi) Written informed consent.
(xii) Inclusion of either trastuzumab and/or taxanes in prior chemotherapy permitted.

Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

(i) Other malignancy within previous 5 years (except carcinoma *in situ* of cervix or basal cell carcinoma).
(ii) A history of CPT-11 use.
(iii) Local and/or general active infectious disease.
(iv) Serious complications such as bleeding in digestive tract, ileus, intestinal paralysis, interstitial pneumonia, pulmonary fibrosis, ischemic heart disease or cardiac dysrhythmia, heart failure, renal failure, hepatic cirrhosis, glaucoma and uncontrolled diabetes mellitus.
(v) Uncontrolled diarrhea.
(vi) A history of severe drug hypersensitivity.
(vii) Middle or large volume of ascites and/or pleural fluid.
(viii) Necessity for continuous administration of steroids.
(ix) Difficulty on registration in this study due to psychological disease.
(x) Central nerve metastasis.
(xi) Need for treatment with atazanavir sulfate.
(xii) Women in pregnancy, at risk of pregnancy or hoping to become pregnant; men who wanted their partners to become pregnant.
(xiii) Patients with active hepatitis type B and/or hepatitis C.
(xiv) Judged to be unsuitable for inclusion in the study by the investigator.

Registration

After written informed consent is obtained, an eligibility report form will be sent to the OGSG Data Center, where

eligible patients will be subsequently enrolled in the trial. Information regarding any necessary follow-up tests will be then sent out from the registration center.

Treatment Methods

Intravenous infusion of CPT-11 every 2 weeks at a dose of 150 mg/m^2; intravenous infusion of trastuzumab at a dose of 8 mg/kg on Day 1 of the first cycle, followed by 6 mg/kg every 3 weeks. Administration of CPT-11 and trastuzumab will be repeated in independent schedules. Treatment will be continued until disease progression, unacceptable toxicity or withdrawal of consent. CPT-11 dose adjustment is allowed according to toxicity. Trastuzumab toxicity is managed by treatment interruption.

Follow-up

Physical and safety evaluations and laboratory tests are performed prior to the initiation of treatment. Responses are evaluated every 2 months or earlier if there are indications of treatment failure due to toxicity. All eligible patients are to be included in the assessment of efficacy and safety. Non-evaluable patients will be added to the efficacy assessment dataset as 'not evaluable. The following dates will be recorded: (i) date of treatment commenced; (ii) date of disease progression; (iii) final date of assessment of survival and (iv) date of death.

Statistical Analysis

The primary endpoint of this study is the DCR, which will be summarized in terms of percentage, with a 95% confidence interval. The DCR is calculated primarily based on the assessment of the central radiologic review. All results will be analyzed in the full analysis set (FAS), which will include all patients, except those deemed to be ineligible after registration. The DCR will be analyzed in the FAS as the primary end point. The sample size of this study will be 30 patients. This sample size provides 80% power under the hypothesis that the expected value of the primary endpoint will be 50% and the threshold value will be 30% using a one-sided exact binomial test at a significance level of 0.10. To evaluate secondary endpoints, the Kaplan–Meier method is analyzed for PFS and OS. An overall response rate and a response rate are summarized in terms of percentage, with a 95% CI.

Monitoring

In-house monitoring will be performed every 6 months by the OGSG Data Center to evaluate study progress and ensure study quality.

Conflict of interest statement

None declared.

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A Phase I Study of Triplet Combination Chemotherapy of Paclitaxel, Cisplatin and S-1 in Patients with Advanced Gastric Cancer

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Objective: S-1 and cisplatin combination therapy is a standard regimen for patients with advanced gastric cancer in Japan. The primary objective of this study was to determine the maximum tolerated dose and dose-limiting toxicities of a triplet regimen adding paclitaxel to S-1 and cisplatin combination therapy.
Methods: Patients with previously untreated metastatic or recurrent gastric cancer were enrolled. Patients received S-1 (40 mg/m^2 p.o., twice daily, on days 1–21 every 35 days), cisplatin (30 mg/m^2 divided, on days 1 and 15) and paclitaxel (divided on days 1 and 15). The starting dose of paclitaxel was 50 mg/m^2 (level 1); the dose was escalated to 60 (level 2), 70 (level 3) and 80 mg/m^2 (level 4) in a stepwise fashion. Dose-limiting toxicity was determined during the first treatment cycle.
Results: Eighteen patients enrolled. During the first cycle, no dose-limiting toxicity was observed at dose levels 1 and 2. At dose level 3, one of the six patients had dose-limiting toxicity (one patient had grade 4 neutropenia) and at dose level 4, one of the six patients had dose-limiting toxicity (one patient had febrile neutropenia, hypoalbuminemia and fatigue of grade 3). The maximum tolerated dose was not reached at level 4; however, grade 3 hyponatremia and hypokalemia in two of the six patients occurred during the second treatment course at level 4. From the point of view of safety in the outpatient setting, the recommended dose of paclitaxel was determined at 70 mg/m^2. The overall response rate was 50%.
Conclusions: The recommended dose of paclitaxel added to S-1 (80 mg/m^2 days 1–21) plus cisplatin (30 mg/m^2 days 1 and 15) was 70 mg/m^2 on days 1 and 15 of a 5-week cycle.

Key words: gastric cancer – paclitaxel – cisplatin – S-1 – triplet combination chemotherapy – phase I

Table 2. Patient characteristics

Age (years)	
Median (range)	61 (34–74)
Gender (male/female)	13/5
ECOG PS	
0	13
1	5
Prior gastrectomy	
−	13
+	5
Histology	
Intestinal type	7
Diffuse type	11
Metastatic site	
Lymph node	15
Liver	5
Peritoneum	6
Distant	2
Target lesion	
−	4
+	14
Treatment cycle	
Median (range)	4 (2–8)

ECOG, Eastern Cooperative Oncology Group.

Table 3. Adverse events during the first cycle

Grade	Level 1 ($n=3$)				Level 2 ($n=3$)				Level 3 ($n=6$)				Level 4 ($n=6$)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	1	2			1				2	2	2			3	1	
Neutropenia	1	1	1		1					1	2	1		1	2	
Anemia	2		1		2				1				2			
Thrombocytopenia	1				1				1				2			
Febrile neutropenia											1				1	
AST/ALT elevation					1				1							
Hypoalbuminemia	1				1				2	1				1	1	
Hypokalemia									1							
Hyponatremia									4							
Anorexia	1	2			1	2			3					3		
Nausea	1		1						1				1	1		
Vomiting	1	1			2	1			1				1			
Diarrhea	1	1			2	1			1				1			
Fatigue		2				2								1	1	
Alopecia	1				1								1			
Allergic reaction									3							
Sensory neuropathy	2								2							
Stomatitis	1															
Rash									1							

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Metastases were identified in the peritoneum in 6 patients, the liver in 5, lymph nodes in 15, bone in 1 and ovary in 1. The total number of treatment courses was 69 (17 cycles at level 1, 12 cycles at level 2, 23 cycles at level 3 and 17 cycles at level 4) and the median number of treatment courses was 4 (range: 2–8).

Toxicities

The toxicities profile during the first course is shown in Table 3. One patient experienced grade 3 neutropenia, hemoglobinemia and nausea, there was no DLT at dose levels 1 and 2. One patient had grade 4 neutropenia and grade 3 febrile neutropenia lasting for 4 days as the DLT at level 3. Three additional patients were assigned to level 3 (total, six patients). Other types of toxicities were grade 3 leukocytopenia and neutropenia. No grade 3 or 4 non-hematologic toxicities were observed. Therefore, the dose of paclitaxel was escalated to level 4. In three patients at level 4, one patient had grade 3 febrile neutropenia lasting for 4 days with fever, hypoalbuminemia and fatigue as the DLT. Three additional patients were assigned to level 4 (total, six patients). Other types of toxicity were grade 3 leukocytopenia, neutropenia and hemoglobinemia. No grade 3 or 4 non-hematologic toxicities, except for hypoalbuminemia and fatigue, were observed.

Neither treatment-related death nor delayed severe toxicities were observed. The toxicities in all treatment courses are summarized in Table 4. Neutropenia was the most commonly observed hematological toxicity. Grade 3 hyponatremia and hypokalemia was seen in two patients for each. Grade 3 fatigue was seen in four patients, anorexia in one patient, diarrhea in one patient and nausea in one patient.

During the first course of treatment, the MTD was not achieved at level 4; however, grade 3 hyponatremia and hypokalemia in two of the six patients occurred during the second treatment course at level 4. From the point of view of safety in the outpatient setting, the protocol committee defined level 4 as the MTD and determined level 3 as the RD.

Efficacy

Of the 18 patients enrolled into this study, 14 patients had measurable metastatic lesions (RECIST). Of these 14 patients, 7 had a partial response, yielding a response rate of 50%, and 7 patients had stable disease (Table 5). The

disease control rate was thus 100%. At a median follow-up of 14.4 months (range: 2.7–52.2), the median OS was 14.2 months (95% confidence interval: 12.5–38.3).

DISCUSSION

S-1 is an oral anticancer drug composed of tegafur and two modulating agents, gimeracil and potassium oxonate, at a molar ratio of 1:0.4:1 (10). Phase II trials of S-1 therapy for advanced gastric cancer performed in Japan have shown a high overall response rate of 44–54% (11, 12). So S-1 has been considered to be a key drug in the treatment of advanced gastric cancer and widely used with or without other drugs in Japan.

CDDP is made of platinum compounds and effective for many types of cancer other than gastric cancer. CDDP as a single agent is reported to be effective for gastric cancer in 22–33% of patients, but is usually used in combination with other anticancer agents (13, 14).

Paclitaxel is a drug extracted from the bark of *Taxus chinensis*, the mechanism of action of which is to promote microtubular protein polymerization and induce stabilization and excessive formation of microtubules to prevent depolymerization of microtubules, resulting in the inhibition of cell division and antitumor activity. It has also been identified as an effective agent for gastric cancer. Phase II studies of paclitaxel monotherapy obtained response rates of 11–23% (15–17).

These drugs have different antitumor mechanisms and several combination regimens containing these drugs have achieved favorable results in patients with unresectable or recurrent gastric cancer. The S-1 plus CDDP regimen has been regarded as the standard regimen in Japan (3). S-1 plus paclitaxel achieved a 48% response rate and paclitaxel plus CDDP also achieved a 43% in a phase II study (18, 19).

Furthermore, triplet chemotherapy is expected to improve the outcomes of advanced unresectable or recurrent gastric cancer patients. In Japanese phase II clinical studies, a triple combination of DCS that included S-1 instead of 5-FU provides a high response rate and long survival of 15 months or longer, but is still associated with a high frequency of grade 4 hematologic toxicity and requires careful management (6, 7). In contrast, triple therapy with paclitaxel has a milder hematologic toxicity compared with DCS regimen. Iwase et al. (8) reported that a phase II clinical study showed a favorable clinical outcome with S-1 (70 mg/m^2, days 1–14), paclitaxel (160 mg/m^2, day 1) and CDDP (60 mg/m^2, day 14) in an every 4-week cycle, with a response rate of 63.5% and the overall survival of 15 months, in which the frequency of serious toxicities was low (grade 4 adverse events

Table 4. Adverse events in all cycles

	Level 1 ($n = 3$)				Level 2 ($n = 3$)				Level 3 ($n = 6$)				Level 4 ($n = 6$)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia			2			1			1	2	3			3	2	
Neutropenia		1	2			1				1	3	1		1	3	
Anemia		1	2		1	1			1	4			1	2	2	
Thrombocytopenia		2			1				2				2			
Febrile neutropenia			1								1				1	
AST/ALT elevation					1				4					1		
Hypoalbuminemia	1				1				2	1				1	1	
Bilirubin	1	1			1				2	1						
Hypokalemia			1						1						2	
Hyponatremia			1		1				4				1		2	
Anorexia		2	1			3			2	2			1	3		
Nausea	1		1						1				1	1		
Vomiting	1	1			2	1			1				1			
Diarrhea	1	1	1		2	1			2	1			1	2		
Fatigue		1	1			2			3		1		1		2	
Alopecia	1	1			3				4					1		
Allergic reaction									3							
Sensory neuropathy	2								2							
Stomatitis	2								1				1	1		
Rash	1	1			1				1							
Edema									1	1			1			

Table 5. Response (RECIST)

Response	Complete response	Partial response	Stable disease	Progressive disease	Response rate (%)	Disease control rate (%)
Overall ($n = 12$)	0	7	7	0	50	100
Level 1 ($n = 2$) (50 mg/m^2)	0	2	1	0	–	–
Level 2 ($n = 2$) (60 mg/m^2)	0	1	1	0	–	–
Level 3 ($n = 3$) (70 mg/m^2)	0	3	1	0	–	–
Level 4 ($n = 5$) (80 mg/m^2)	0	1	4	0	–	–

RECIST, Response Evaluation Criteria in Solid Tumors.

included neutropenia [7.9%], thrombocytopenia [1.6%] and decreased hemoglobin [1.6%]) and grade 3 or greater non-hematologic toxicities were not observed. The phase II clinical study performed by J.Y. Kim et al. (20) also showed a good clinical outcome with a divided dose regimen, in which the doses of paclitaxel and CDDP in the regimen used by Iwase et al. (8) were divided into 80 and 30 mg/m^2, respectively and administered at two time points, days 1 and 14 of every 4-week cycle. Grade 4 adverse events included leukocytopenia (4.8%) and neutropenia (19.0%) and Grade 3 non-hematologic toxicities occurred in 2–5%. The response rate was 59.1% and the overall survival was 11.2 months.

Several phase II studies have reported that the toxicity of triple combination therapy can be reduced by dividing the dose of CDDP into 20–40 mg/m^2 weekly or biweekly, leading to a decrease in adverse events and the continuity of the treatment while maintaining efficacy (20–23). If one can administer CDDP with the dose divided into two equal doses while maintaining its dose intensity, patients no longer require a large amount of infusion or inpatient care, resulting in improved quality of life.

In this study, we divided CDDP into 30 mg/m^2 on days 1 and 15 while the dose intensity of CDDP of the standard SP regimen was maintained. By virtue of division of the CDDP dose, non-hematological toxicities were mild, and the dose of paclitaxel could subsequently be increased to 80 mg/m^2 at level 4. Grade 3 febrile neutropenia was observed in one patient at levels 3 and 4 as the DLT. Except for nausea at level 1 and hypoalbuminemia and fatigue at level 4, no grade 3 or 4 non-hematologic toxicities were observed during the first course. On the other hand, grade 3 non-hematological toxicities, such as fatigue, hyponatremia and hypokalemia were observed during the second treatment course at level 4. In view of safety and continuity in the outpatient setting, we defined the MTD of this triplet regimen as level 4 and the RD as level 3.

In this study, we recommended inpatient treatment during the initial treatment course for safety reasons, but the second or later courses of treatment could be administered safely on an outpatient basis because inpatient hydration was not required, and no TLD was observed. Based on the severity and frequency of adverse events, this regimen was considered to be a promising treatment option that is safe, highly manageable and can be administered as outpatient therapy.

Among 14 patients with RECIST-evaluable lesions, 7 patients achieved PR and 7 patients SD, with a response rate of 50% and a disease control rate of 100%. As with other PCS therapies, the response rate was slightly lower when compared with DCS, but three of the four patients demonstrated tumor response at the RD of paclitaxel of 70 mg/m^2, showing that the therapy provides sufficient efficacy.

In conclusion, the RD of the PCS regimen is as follows: S-1 80 mg/m^2 on days 1–21, CDDP 30 mg/m^2 and PTX 70 mg/m^2 on days 1 and 15 of a 5-week cycle. We are conducting a phase II study using the response rate as a primary endpoint and expecting promising results for this approach as a triple-agent therapy that can be administered on an outpatient basis.

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Conflict of interest statement

None declared.

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