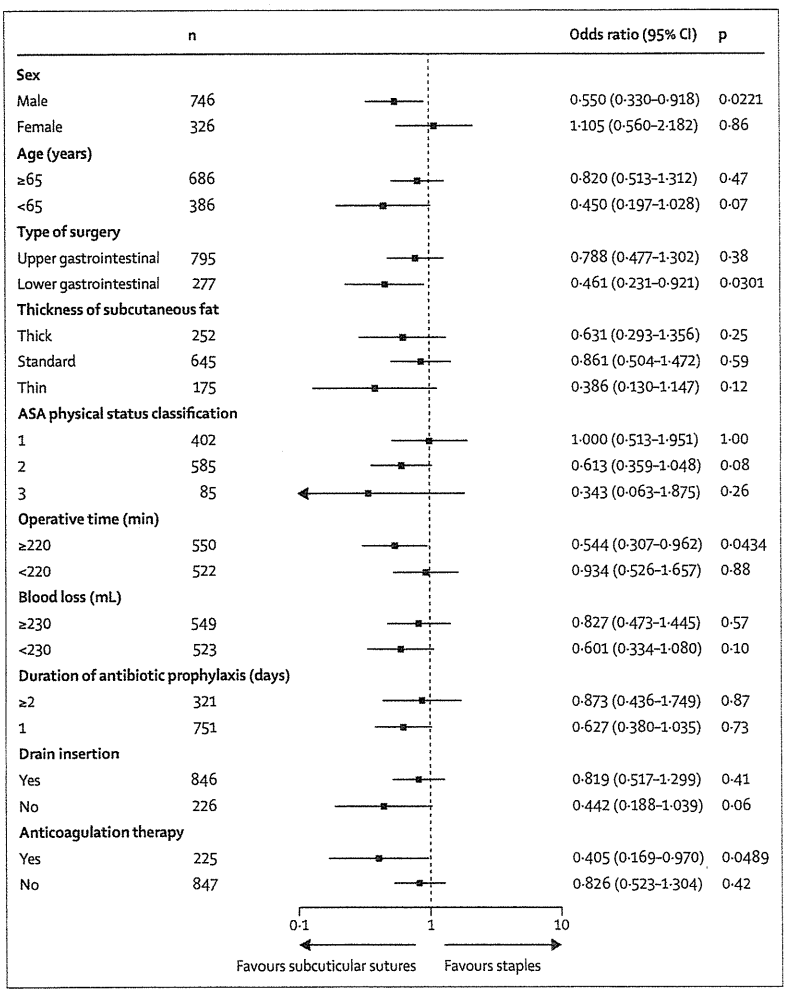

Figure 2: **Subset analysis of wound complications in the modified intention-to-treat population**
Significance was calculated with Fisher's exact test. ASA=American Society of Anesthesiologists.

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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For more on **Media Planning** see http://www.mediapng.co.jp

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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

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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

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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

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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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Original Articles

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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Intraoperative versus extended antimicrobial prophylaxis after gastric cancer surgery: a phase 3, open-label, randomised controlled, non-inferiority trial

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Summary

Background Although evidence for the efficacy of postoperative antimicrobial prophylaxis is scarce, many patients routinely receive such treatment after major surgeries. We aimed to compare the incidence of surgical-site infections with intraoperative antimicrobial prophylaxis alone versus intraoperative plus postoperative administration.

Methods We did a prospective, open-label, phase 3, randomised study at seven hospitals in Japan. Patients with gastric cancer that was potentially curable with a distal gastrectomy were randomly assigned (1:1) to receive either intraoperative antimicrobial prophylaxis alone (cefazolin 1 g before the surgical incision and every 3 h as intraoperative supplements) or extended antimicrobial prophylaxis (intraoperative administration plus cefazolin 1 g once after closure and twice daily for 2 postoperative days). Randomisation was stratified using Pocock and Simon's minimisation method for institution and American Society of Anesthesiologists scores, and Mersenne twister was used for random number generation. The primary endpoint was the incidence of surgical-site infections. We assessed non-inferiority of intraoperative therapy with a margin of 5%. Analysis was by intention-to-treat. During hospital stay, infection-control personnel assessed patients for infection, and the principal surgeons were required to check for surgical-site infections at outpatient clinics until 30 days after surgery. This study is registered with UMIN-CTR, UMIN000000631.

Findings Between June 2, 2005, and Dec 6, 2007, 355 patients were randomly assigned to receive either intraoperative antimicrobial prophylaxis alone (n=176) or extended antimicrobial prophylaxis (n=179). Eight patients (5%, 95% CI 2–9%) had surgical-site infections in the intraoperative group compared with 16 (9%, 5–14) in the extended group. The relative risk of surgical-site infections with intraoperative antimicrobial prophylaxis was 0·51 (0·22–1·16), which revealed statistically significant non-inferiority ($p<0·0001$).

Interpretation Elimination of postoperative antimicrobial prophylaxis did not increase the incidence of surgical-site infections after a gastrectomy. Therefore, this treatment is not recommended after gastric cancer surgery.

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Introduction

The Centers for Disease Control and Prevention in the USA has issued guidelines that recommend administration of a first-generation cephalosporin for intraoperative antimicrobial prophylaxis to prevent surgical site infections in clean or clean-contaminated operations.[1] This treatment is usually given within 30 min of the first surgical incision, with supplementary treatments every 3 h or 4 h throughout the operation.[2] Results of a large-scale national cohort study in the USA showed that only 14·5% of 32 603 patients who had major surgery had discontinued antimicrobial prophylaxis within 12 h after the surgery ended and that 26·7% of patients were still receiving this treatment at 48 h after surgery.[3] Furthermore, a questionnaire administered to 3823 Japanese surgeons showed that 56·4% of them gave antimicrobial prophylaxis in clean-contaminated operations until 3–4 days after surgery, whereas only 2·4% of surgeons gave the treatment for 24 h or less after surgery ended.[4] Because of a high prevalence of drain use in gastrointestinal surgery in Japan and the potential risk of surgical-site infections, the Japanese Association for Infectious Diseases and the Japanese Society of Chemotherapy developed guidelines that recommend postoperative antimicrobial prophylaxis for 1–3 days after gastrointestinal surgery.[5] However, postoperative antimicrobial prophylaxis is controversial because evidence for its efficacy is scarce.

Gastric cancer is the third leading cause of cancer deaths worldwide and the most common in eastern Asia. Surgery for gastric cancer is usually accompanied by extended lymph node dissection, known as a D2 lymphadenectomy.[6] The Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) did a preliminary multicentre phase 2 trial (OGSG0202)[7] to examine the clinical outcomes when postoperative antimicrobial prophylaxis is not given to patients with gastric cancer. 56 patients who were scheduled to have a distal gastrectomy were registered in this study. Cefazolin was given 30 min before the skin incision and every 3 h during the operation without postoperative antimicrobial prophylaxis. Surgical-site infections were recorded in three patients (5·4%), which was similar to the prevalence in historical controls who had received postoperative antimicrobial prophylaxis (6·7%).[7] After the

phase 2 trial, we designed this multicentre, randomised, phase 3 trial (OGSG0501) to assess non-inferiority of the omission of postoperative antimicrobial prophylaxis in patients with gastric cancer.

Methods

Patients

We enrolled patients who had histologically proven gastric adenocarcinoma that was deemed curable with a distal gastrectomy. Patients were also required to have an American Society of Anesthesiologists (ASA) score of 1 or 2. Patients were excluded from the study if they had an active or uncontrolled infection, received neoadjuvant chemotherapy, or had been given steroids. Seven institutions of the OGSG in Japan participated in the trial. The study protocol was approved by the OGSG Steering Committee and the institutional review boards of all of the participating hospitals. All patients provided written informed consent before randomisation. This study was registered with UMIN-CTR, UMIN000000631.

For the **UMIN-CTR database** see http://www.umin.ac.jp/ctr/

***Panel 1:* Definitions of surgical-site infections[1]**

Superficial incisional

Infection occurs within 30 days after the operation and involves only skin or subcutaneous tissue of the incision and at least one of the following:

- 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;
- at least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.

Deep incisional

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection seems to be related to the operation. The infection involves deep soft tissues (eg, fascial and muscle layers) of the incision and at least one of the following:

- purulent drainage from the deep incision but not from the organ or space component of the surgical site;
- a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localised pain, or tenderness, unless site is culture-negative;
- an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiological examination.

Organ or space

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection seems to be related to the operation. The infection involves any part of the anatomy (eg, organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

- purulent drainage from a drain that is placed through a stab wound into the organ or space;
- organisms isolated from an aseptically obtained culture of fluid or tissue in the organ or space;
- an abscess or other evidence of infection involving the organ or space that is found on direct examination, during reoperation, or by histopathological or radiological examination.

Randomisation and masking

After confirming the eligibility of patients during surgery, surgeons contacted the OGSG data centre by telephone to receive a randomly generated assignment (1:1) placing the patients in one of the treatment groups. We used Pocock and Simon's minimisation method to stratify treatment groups according to institution and ASA scores, and Mersenne twister for random number generation.[8] The surgeon gave the assigned treatment. Interventions were not masked. The OGSG data centre was responsible for assigning the intervention, data management, central monitoring, and statistical analyses.

Procedures

For both groups, the surgeon did distal gastrectomies and lymphadenectomies according to Japanese Gastric Cancer Treatment Guidelines.[9] In short, D1 lymphadenectomy plus suprapancreatic node dissection (D1+β dissection) was done for patients with cT1 tumours, whereas D2 lymphadenectomy was done for patients with cT2–4 tumours. The reconstruction method and the surgical approach (open or laparoscopic) were not prespecified.

1 g of cefazolin was given 30 min after anaesthesia, and an additional dose was given every 3 h during surgery. For the extended antimicrobial prophylaxis group, 1 g of cefazolin was given on postoperative day 0 (at night) and every 12 h until postoperative day 2 (2 g per day for 2 postoperative days). Care before and after surgery and wound management were done according to respective institutional standards.

Operative methods and pathology results were recorded according to the 13th edition of the Japanese Classification of Gastric Carcinoma.[10] The prognostic nutritional index was calculated as: 0·005×lymphocyte count (cells per μL)+10×serum albumin (g/dL).[11] Infection control personnel monitored and detected surgical-site infections during the patient's hospital stay. Principal surgeons were required to check for the presence or absence of surgical-site infections at outpatient clinics until 30 days after surgery. The Centers for Disease Control and Prevention's National Nosocomial Infection Surveillance system was used to diagnose surgical-site infections (panel 1),[1] which were classified as superficial incisional, deep incisional, and organ or space.

Statistical analysis

The primary endpoint was the incidence of surgical-site infections. Secondary endpoints were the incidence of infection at remote sites, the incidence of fever higher than 38°C, body temperature on postoperative day 3, duration of hospital stay after surgery, and severe adverse reactions to antimicrobial prophylaxis.

We intended to recruit 342 patients with a power of 80% for the Dunnet–Gent test at a one-sided α of 0·05 to show non-inferiority of incidence of surgical-site infections. This allowed us to detect a non-inferiority margin of 5% for incidence of surgical-site infections in the intraoperative antimicrobial prophylaxis group with an estimation of a 6·7% incidence of these infections in the extended treatment group. The projected accrual period was 3 years, and no interim analysis was planned.

For secondary endpoints, we compared binary variables with Fisher's exact test, and continuous variables with the Mann-Whitney *U* test. Logistic regression analysis was done to adjust for potential confounding factors, including age, sex, lymphadenectomy, reconstruction method, postoperative cancer stage, body-mass index, prognostic nutritional index, and transfusions. Nine subgroups were also analysed with logistic regression to assess statistical interactions between the treatment and various subgroups. Because of the exploratory nature of subgroup comparisons, test results are reported without multiplicity adjustment of type I error.

Because the study was designed to use a one-sided test, we present one-sided p values for the primary analysis results of the non-inferiority test of surgical-site infections. Two-sided p values were calculated for all other tests. All p values less than 0·05 were judged to be statistically significant. Analysis was by intention-to-treat. Statistical analyses were done with SPSS version 17.0 and R version 2.12.2.

Role of the funding source

This study was funded by OGSG, which is a non-profit organisation established to develop cancer treatment. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 2, 2005, and Dec 6, 2007, 355 patients from seven hospitals were randomly assigned: 176 to receive intraoperative antimicrobial prophylaxis, and 179 to the extended antimicrobial prophylaxis group (figure 1). Two patients underwent a total gastrectomy because they had a positive resection margin, and one had palliative bypass surgery with gastrointestinal anastomosis. All patients received all planned antimicrobial doses and were monitored during their hospital stay and until 30 days after surgery. No severe adverse reactions to antimicrobial prophylaxis occurred in either group.

The patients' characteristics in the two groups were well balanced (table 1). Median body-mass index and median prognostic nutritional index were much the same between the two groups. About 60% of patients in both groups had early (T1) gastric cancer. A D2 or more extended lymphadenectomy was done in 123 patients assigned to the intraoperative antimicrobial prophylaxis group (70%) and in 120 patients assigned to the extended antimicrobial prophylaxis group (67%). The between-group differences in median operation time was 9 min and in median blood loss was 10 mL. 14 patients had laparoscopy-assisted distal gastrectomy.

24 patients had surgical-site infections (table 2), all of whom had undergone distal gastrectomy without protocol violation. The incidence of surgical-site infections was 5% (95% CI 2–9%) in the intraoperative antimicrobial prophylaxis group compared with 9% (5–14%) in the extended antimicrobial prophylaxis group. Intraoperative administration was non-inferior to postoperative treatment (one-sided p<0·0001). On the basis of a multiple logistic regression analysis, the odds ratios (ORs) for surgical-site infections with intraoperative antimicrobial prophylaxis was 0·49 (95% CI 0·20–1·16) before and 0·55 (0·21–1·45) after adjusting for eight variables (age, sex, lymphadenectomy, reconstruction method, postoperative cancer stage, body-mass index, prognostic nutritional index, and transfusions).

Most surgical-site infections involved organ or space, and no deep incisional infections arose (table 2).

We assessed statistical interactions between the treatment effects and patient characteristics, including body-mass index, prognostic nutritional index, and operation time (figure 2). No subgroups showed a decrease in the incidence of surgical-site infections with extended antimicrobial prophylaxis. The OR for surgical site infections with intraoperative antimicrobial prophylaxis was 0·31 (95% CI 0·099–0·998; p=0·050) for patients who were not overweight (body-mass index <25)

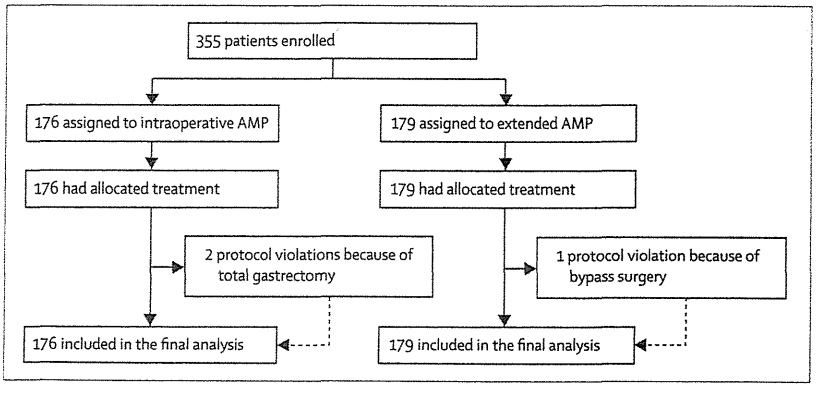

Figure 1: **Trial profile**
AMP=antimicrobial prophylaxis.

	Intraoperative AMP (n=176)	Extended AMP (n=179)
Age (years)	66 (36–84)	65 (35–84)
Sex		
Male	115	125
Female	61	54
Lymphadenectomy		
D1*	53	59
D2–3	123	120
Reconstruction method		
Billroth-I	83	103
Billroth-II	3	1
Roux-Y	90	75
pT stage		
T1	104	111
T2	46	42
T3–4	26	26
pN stage		
N0	114	122
N1	38	36
N2–3	24	21
Body-mass index	22·3 (16·3–33·0)	22·5 (12·4–32·9)
Prognostic nutrition index†	51·1 (25·1–68·9)	51·7 (26·6–66·0)
Approach		
Open	169	172
Laparoscopic	7	7
Anastomotic method		
Hand-sewn	21	34
Autosuture	119	119
Mixed	36	26
Drainage tube		
Yes	157	153
No	19	26
Operation time (min)	209 (58–428)	200 (64–415)
Blood loss (mL)	200 (1–880)	210 (1–1700)
Transfusion		
Yes	0	4
No	176	175

Data are number or median (range). AMP=antimicrobial prophylaxis. pT=primary tumour. pN=lymph node status. *One patient in the extended AMP group who underwent palliative bypass surgery was included in D1. †Data from 28 patients in the intraoperative AMP group and 23 patients in the extended AMP group are missing.

Table 1: **Characteristics of patients**

	Intraoperative AMP (n=176)	Extended AMP (n=179)	Relative risk (95% CI)	p value*
Surgical-site infections	8 (5%)	16 (9%)	0·51 (0·22–1·16)	0·138
Superficial incisional	1 (<1%)	5 (3%)	..	0·215
Deep incisional	0	0	..	..
Organ or space	7 (4%)	11 (6%)	..	0·469
With anastomotic leakage	1	4	..	..
Without anastomotic leakage	6	7	..	..

AMP=antimicrobial prophylaxis. *Two-sided p value for superiority test.

Table 2: **Incidence of surgical-site infections**

and 1·09 (0·25–4·72; 0·91) for patients who were overweight (body-mass index ≥25).

All secondary endpoints were compared between the intraoperative antimicrobial prophylaxis group and extended administration group (table 3). The incidence of remote site infections was 5% (95% CI 2–10) with intraoperative antimicrobial prophylaxis and 3% (1–7) with extended treatment. For remote site infections, two patients had pneumonia or bronchitis and one patient had a urinary tract infection in each group. The incidence of fever higher than 38°C was 34% (27·1–41·6) and 29% (22·5–36·3) in the intraoperative and extended groups, respectively. Median body temperature on postoperative day 3 was about 37°C in both groups and median duration of hospital stay was 12 days with both treatments.

Discussion

Omitting postoperative antimicrobial prophylaxis does not increase the incidence of surgical-site infections in patients with gastric cancer. Extended antimicrobial prophylaxis is associated with greater costs than intraoperative treatment alone because of the use of unnecessary drugs and might increase the risk of adverse drug reactions. Additionally, shortening of the antimicrobial prophylaxis period could help prevent the emergence of resistant strains.[12,13] For these reasons, we do not recommend antimicrobial prophylaxis after gastric cancer surgery.

In a US study, about 60% of patients who had had major surgery were still receiving antimicrobial prophylaxis at 24 h after surgery.[3] Results of a survey of 14 high-volume hospitals in South Korea and Japan showed that at 11 institutions antimicrobial prophylaxis was routinely given for longer than 24 h.[14] Although the national surgical infection prevention guidelines in the USA recommend that this treatment should be discontinued within 24 h of surgery,[15] this approach has not yet been adopted worldwide, because the recommendation is not based on clear evidence. Previously, the standard surgical treatment for gastric cancer was extended D2 lymphadenectomy in eastern Asia,[6,16] but was limited to D0 or D1 lymphadenectomy in the USA and Europe.[17,18] However, in 2010, the European Society for Medical Oncology guidelines for gastric cancer[19] were revised and they now recommend an extended D2 lymphadenectomy as the standard procedure, as in Japanese guidelines. Furthermore, in the latest version (2.2011) of the National Comprehensive Cancer Network Guidelines for gastric cancer, an extended D2 lymphadenectomy was recommended in the USA.[20] Therefore, the question of the appropriate length of antimicrobial prophylaxis after an extended D2 gastrectomy is relevant worldwide.

Mohri and colleagues[21] reported that the incidence of surgical-site infection in gastric cancer surgery was much the same (9·5% *vs* 8·6%) for single-dose and multiple-dose antimicrobial prophylaxis, although their study did not fix the type of surgery and the antibiotics to a single

drug (panel 2). Other retrospective studies have reported incidences of surgical-site infections of 8–12% after a gastrectomy.[23,24] In our phase 3 study, the overall incidence of these infections was 5% in the intraoperative antimicrobial prophylaxis group, which was much the same as the incidence in our previous phase 2 trial (5·4%). The Japanese health system is a suitable setting in which to assess the frequency of surgical-site infections because Japanese institutions allow a long hospital stay after surgery. The median length hospital stay after surgery was 12 days in each group, which enabled infection control personnel to accurately assess the incidence of surgical-site infections for almost half of the follow-up period. Our study required the principal surgeons to check for the presence or absence of surgical-site infections at outpatient clinics until 30 days after surgery. Systematic measurement instruments, which are independent of principal investigators, often result in an underestimation of the incidence of surgical-site infections.[25] Therefore, our results are likely to be an accurate assessment of the frequency of surgical-site infections after a distal gastrectomy.

Several factors such as obesity, malnutrition, transfusions, and operation time increase the incidence of surgical-site infections.[23,26–29] In this study, body-mass index, prognostic nutritional index, and operation time were much the same between the two groups. However, the number of patients who required a transfusion differed between the two groups (none in the intraoperative group and four in the extended group). Of the four patients who received a transfusion, one had an organ or space surgical-site infection after the gastrectomy, which might have led to the unexpected result that the incidence of surgical-site infections was higher in the extended antimicrobial prophylaxis group than in the intraoperative administration group. However, after adjusting for all the potential confounding factors including transfusions by a multivariate analysis, the OR for surgical-site infection with intraoperative antimicrobial prophylaxis was essentially unchanged (0·49 before adjustment *vs* 0·55 after adjustment). An Italian small-scale randomised study[22] that included patients with gastric cancer and colorectal cancer reported that the incidence of surgical-site infections was 16·1% in the intraoperative antimicrobial prophylaxis group and 44·0% in the extended administration group (panel 2). These results and ours suggest that elimination of postoperative antimicrobial prophylaxis might in fact reduce the risk of such infections, although our study was not planned to assess superiority.

The incidence of surgical-site infections in patients who were not overweight (body-mass index <25) was significantly higher in the extended group than in the intraoperative group (p=0·05), whereas the incidence of these infections in patients who were overweight (body-mass index ≥25) was almost same between the two groups (p=0·91). Why postoperative antimicrobial prophylaxis significantly increased the incidence of surgical-site infections in patients who were not overweight is unclear. In the additional analysis in this

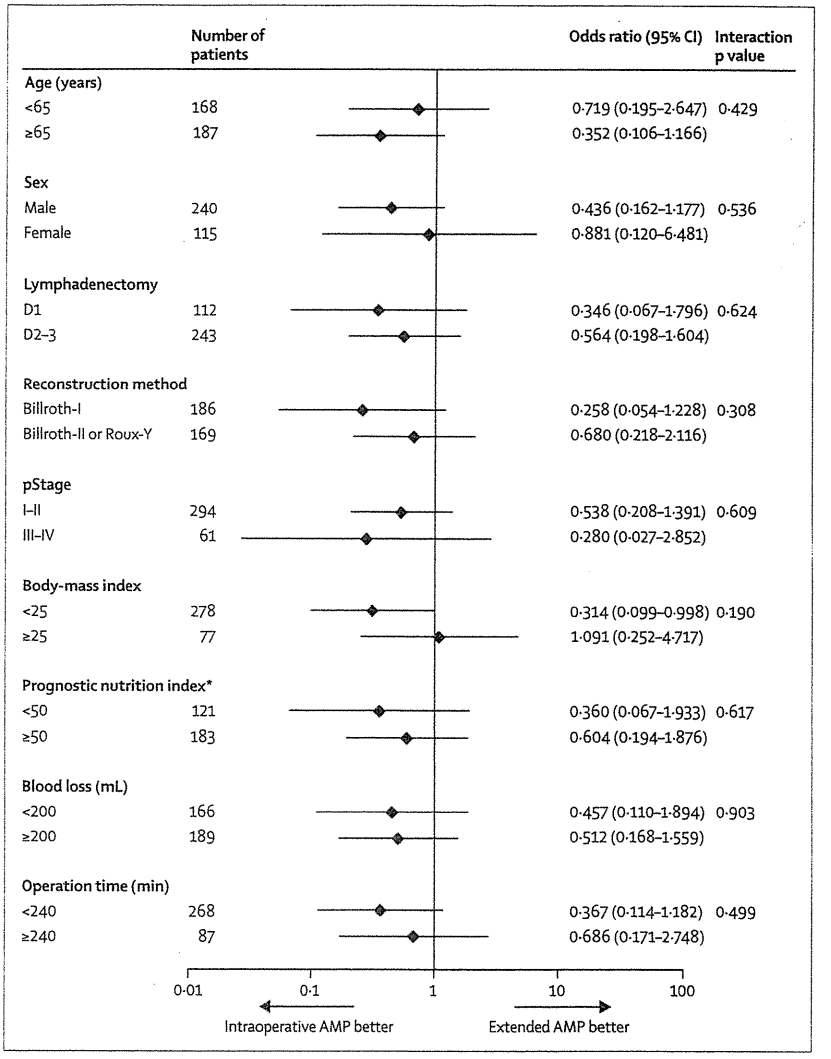

Figure 2: **Forest plot of subgroup analyses**
p values for interactions and odds ratios for surgical-site infections with intraoperative antimicrobial prophylaxis (AMP).*Data for prognostic nutrition index from 51 patients are missing.

	Intraoperative AMP (n=176)	Extended AMP (n=179)	Relative risk (95% CI)	p value
Remote site infections	..	..	1·53 (0·56–4·20)	0·441
Yes	9	6	..	
No	167	173	..	
Fever higher than 38°C	60	52	1·17 (0·86–1·60)	0·361
Body temperature on POD 3 (°C)	37·0 (35·7–40·0)	36·9 (35·3–39·1)	..	0·145
Duration of hospital stay after surgery (days)	12 (7–114)	12 (7–87)	..	0·742

Data are number or median (range) unless otherwise specified. AMP=antimicrobial prophylaxis. POD=postoperative day.

Table 3: **Secondary endpoints**

Panel 2: Research in context

Systematic review

We searched PubMed with the terms "gastric cancer", "surgery", and "antibiotics". Two randomised controlled studies[21,22] including patients with gastric cancer have been reported. A small-scale study in Italy[22] included both patients with gastric cancer and those with colorectal cancer and compared 1-day antimicrobial prophylaxis with clindamycin plus gentamicin to 7-day antimicrobial prophylaxis with ampicillin. A Japanese study compared intraoperative antimicrobial prophylaxis to intraoperative plus postoperative (until 3 postoperative days) treatment with cefazolin or ampicillin-sulbactam.[21] Neither study fixed the type of surgery or the antibiotics to a single agent.

Interpretation

Most of the previous studies used as the basis for the US Centers for Disease Control and Prevention guidelines did not include patients with gastric cancer. Because of absence of strong evidence to show that intraoperative administration of antimicrobial prophylaxis is sufficient to prevent surgical-site infections after D2 gastrectomy, antimicrobial prophylaxis is commonly prescribed for more than 24 h to prevent postoperative complications. Our multicentre study group did a phase 2 study to assess the feasibility of intraoperative antimicrobial prophylaxis alone and to confirm the prevalence of surgical-site infections after distal gastrectomy.[7] This is the first phase 3 study to assess the effectiveness of a fixed regimen for postoperative antimicrobial prophylaxis after distal gastrectomy. Our results show that postoperative antimicrobial prophylaxis is not recommended for patients with gastric cancer even after extended lymphadenectomy.

subgroup, patients who were underweight (body-mass index <18·5) and those of normal weight (body-mass index ≥18·5 and <25) had much the same OR for surgical-site infections (underweight 0·36, 95% CI 0·03–4·50; normal weight 0·29, 0·078–1·08). This result could be a false positive resulting from multiple testing. However, this does not affect the most important findings, which are that extended antimicrobial prophylaxis did not decrease the incidence, even in high-risk subgroups, such as patients with a high body-mass index, low prognostic nutritional index, or long operation time.

Our study included only patients with gastric cancer undergoing a distal gastrectomy. A total gastrectomy is usually associated with greater blood loss and a longer operation time than a distal gastrectomy. Because extended antimicrobial prophylaxis was not beneficial in this study, even in subgroups with a long operation time or much blood loss, we believe that our conclusion can be applied to patients with gastric cancer who are undergoing a total gastrectomy and therefore have a similar microflora in the operative field. However, our findings might not apply to patients who require surgery for other organs such as the colon or hepatobiliary tract because of differences in the microflora in the operative field and the baseline incidence of surgical-site infections.[24,30] Further studies are needed to assess postoperative antimicrobial prophylaxis with surgeries that typically have an increased incidence of surgical-site infections.

In three patients who had protocol violations, no surgical-site infections were recorded. Therefore, per-protocol analysis excluding these three patients gave much the same results as the intention-to-treat analysis. One of the limitations of our study was the absence of blinding. We did not use a placebo in this study, and surgeons and care providers were not masked to treatment allocation. The protocol did not specify that patients should be told about their allocation, so that whether they were masked to their treatment group is uncertain. However, during hospital stay, the assessment of surgical-site infections was done by infection control personnel who were not involved in this study. Therefore, we feel the possibility of a bias in assessment of endpoints is negligible.

Contributors

HI and HF conceived and designed the trial. Data collection and statistical analyses were done by TS. YKu and TT drafted the paper. KI, YKi, and SI revised the paper. All authors approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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Optimal indications for second-line chemotherapy in advanced gastric cancer

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As it remains uncertain whether patients with advanced gastric cancer who progress after first-line chemotherapy should receive second-line chemotherapy, we attempted to identify the optimal indications for second-line chemotherapy. In this retrospective study, 101 patients were included in univariate and multivariate analyses to identify clinicopathological variables independently associated with longer survival postprogression (SPP), defined as the time from recognition of disease progression on first-line chemotherapy to death from any cause or last follow-up. The median SPP was 340 days. On multivariate analysis, performance status 2 [hazard ratio (HR), 14.234; 95% confidence interval (CI), 2.766–73.258], serum albumin level less than 3.5 g/dl (HR, 2.088; 95% CI, 1.047–4.060) at initiation of second-line chemotherapy, and time to progression less than 170 days on first-line chemotherapy (HR, 2.497; 95% CI, 1.227–5.083) were identified as independent prognostic factors associated with shorter SPP. The median SPP was 496, 375, and 232 days in patients with 0, 1, and 2 of these 3 negative prognostic factors, respectively ($P=0.0002$). The present study suggests that second-line chemotherapy would not be beneficial in patients with two or more of the following three negative prognostic factors: performance status 2, serum albumin less than 3.5 g/dl at initiation of second-line chemotherapy and time to progression less than 170 days on first-line chemotherapy. *Anti-Cancer Drugs* 23:465–470 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: advanced gastric cancer, indication, prognostic factor, second-line chemotherapy

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Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide, despite a recent decline in its global incidence [1–3]. Surgical resection is the mainstay of curative treatment for gastric cancer; however, the disease is often too advanced at initial diagnosis to allow for curative surgery. For such patients, the goals of chemotherapy are symptom palliation and prolongation of survival [4]. Despite considerable efforts to develop effective chemotherapy regimens, advanced gastric cancer (AGC) remains a challenging malignancy, with a median survival of 9–13 months [5–8]. Although there are no globally accepted standard regimens for AGC, doublet combinations containing 5-fluorouracil or oral fluoropyrimidines such as S-1 and capecitabine with platinum agents are the most commonly used first-line treatments worldwide [5,7,9]. In Japan, other regimens such as S-1 plus irinotecan [10], S-1 plus a taxane (paclitaxel or docetaxel) [11,12], and irinotecan plus cisplatin [8] have also been vigorously evaluated as first-line treatment in phase II/III trials. In addition, triplet regimens consisting of S-1, cisplatin, and a taxane have recently shown promising results, with a median survival over 15 months [13–15].

Although first-line chemotherapy effectively reduces tumor size in approximately half of patients with AGC, it ultimately fails and leads to disease progression after 4–6 months [5–8]. Whether every patient who progresses after first-line chemotherapy should go on to receive second-line chemotherapy remains under debate. In Japan, Korea, and Italy, on the basis of the results of several studies on second-line chemotherapy [16–20], more than half of patients with AGC receive second-line treatment in clinical practice [21]. Taxanes and irinotecan are the most commonly used agents as second-line chemotherapy [16–20,22]. Recently, in a small randomized phase III study with 40 patients with AGC, best supportive care (BSC) plus second-line irinotecan improved overall survival (OS) over BSC alone [23]. However, patient selection for second-line chemotherapy remains uncertain. Several factors such as performance status (PS), extent of disease, cumulative toxicity of the first-line treatment, history of the agents used, and efficacy of first-line chemotherapy should be taken into consideration when selecting patients who are likely to benefit from second-line chemotherapy [21]. We therefore attempted to identify the optimal indications for second-line chemotherapy in patients with AGC.

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Patients and methods

Patients

Of the 157 patients with primary unresectable or recurrent gastric cancer treated at our institution between April 2000 and January 2010, 101 fulfilled the following inclusion criteria for this retrospective study: (a) histologically proven unresectable or recurrent gastric adenocarcinoma; (b) treatment with second-line chemotherapy after first-line chemotherapy failed; (c) maximum Eastern Cooperative Oncology Group PS of 2 at initiation of second-line chemotherapy; (d) adequate bone marrow function (white blood cell count 3000–12 000 mm^{-3}, platelet count $\geq$ 100 000 mm^{-3}, and hemoglobin $\geq$ 8.0 g/dl), hepatic function (total bilirubin $\leq$ 1.5 mg/dl, serum transaminases $\leq$ 100 U/l), and renal function (serum creatinine $\leq$ upper institutional limit) at initiation of second-line chemotherapy; and (e) no other concurrently active malignancies.

Overall survival and efficacy of first-line chemotherapy

Survival postprogression (SPP) was defined as the time from disease progression on first-line chemotherapy to death from any cause or last follow-up. Time to progression (TTP) on first-line chemotherapy was defined as the interval between initiation of first-line chemotherapy and recognition of disease progression.

During first-line chemotherapy, each patient with a measurable lesion was assessed for response according to the Response Evaluation Criteria in Solid Tumors [24], with computed tomography (CT) scans performed every 2 or 3 months until disease progression. Patients with only nonmeasurable lesions were considered to have stable disease (SD) if neither complete disappearance (CR) nor obvious progression (PD) of the recurrent disease was observed on CT scans.

Statistical analysis

SPP and TTP were calculated using the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to identify clinicopathological variables independently associated with SPP. Hazard ratios (HR) and 95% confidence intervals (CI) were also calculated. *P*-values less than 0.05 were considered statistically significant and all *P*-values correspond to two-sided significance tests. All statistical analyses were carried out using SAS statistical software 5.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

The clinicopathological characteristics of the 101 patients at the initiation of second-line chemotherapy are shown in Table 1. There were 68 men and 33 women, with a median age of 69 (range, 25–85) years. The majority of patients had a good PS (0 or 1); there were five patients with PS 2. Histologically, 43 patients had intestinal-type adenocarcinoma and 58 had diffuse-type adenocarcinom Fifty-two patients had primary unresectable gastr cancer and 49 had recurrent disease. There were patients with measurable metastatic lesions, and multip metastatic sites were present in 13 patients. Sixty-tv patients had serum albumin (Alb) levels of 3.5 g/dl greater, and 84 patients had C-reactive protein (CRI values below 1.0 mg/dl, whereas 33 patients were anemi with hemoglobin (Hb) less than 10 g/dl.

Table 1 Patient characteristics at initiation of second-line chemotherapy

Number of patients	101
Sex (males/females)	68/33
Age (years), median (range)	69 (25–85)
ECOG performance status	
0–1/2	96/5
Histology (Lauren classification)	
Intestinal/diffuse	43/58
Primary tumor	
Present/absent	52/49
Site of primary tumor	
Cardia/body/antrum/total	14/40/44/3
Measurable lesion	
Present/absent	61/40
Number of metastatic sites	
1/ $\geq$ 2	88/13
Metastatic site	
Lymph node/liver/peritoneum/lung/bone/brain	31/30/42/7/3
Serum albumin (Alb)	
<3.5 g/dl/ $\geq$ 3.5 g/dl	39/62
C-reactive protein (CRP)	
<1.0 mg/dl/ $\geq$ 1.0 mg	84/17
Hemoglobin (Hb)	
<10 g/dl/ $\geq$ 10 g/dl	33/68

ECOG, Eastern Cooperative Oncology Group.

Chemotherapy regimens

Table 2 summarizes the first-line and second-lir chemotherapy regimens that the patients received. Mo patients (96/101) received S-1-based regimens, with fi patients treated with irinotecan plus cisplatin. Tl majority of patients were participants in clinical tria who were treated according to trial protocols. Chemothe apy regimens for nontrial participants were based on tl treating physician's discretion.

Second-line regimens included S-1-based regimens (41 taxane monotherapy (30), irinotecan-based regime (29), and cisplatin plus paclitaxel (1).

Survival time postprogression

The median follow-up for all 101 patients was 490 day Seventy-one deaths occurred during the study perio The median SPP was 340 days, as shown in Fig. 1. Tl median TTP on first-line chemotherapy was 178 day The median SPP was significantly longer in the patients with TTP $\geq$ 170 days (median, 434 days) tha in the 47 patients with TTP < 170 days (median, 2 days) ($P = 0.0087$), as shown in Fig. 2.

On first-line chemotherapy, six patients achieved CR ar 38 patients achieved a partial response (PR). SD w

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