**Table 2** Frequency of common toxicities ($n$=51: maximum toxicity per patient)

| Adverse event | All grades $n$ (%) | Grade 3 | Grade 4 | ≥ Grade 3 (%) |
|---|---|---|---|---|
| Hematological | | | | |
| Leukopenia | 14 (27.5) | 1 | 0 | (2.0) |
| Neutropenia | 16 (31.4) | 3 | 1 | (7.8) |
| Thrombocytopenia | 13 (25.5) | 0 | 0 | (0) |
| Anemia | 45 (88.2) | 0 | 1 | (2.0) |
| Non-hematological | | | | |
| Peripheral neuropathy | 22 (43.1) | 2 | 0 | (3.9) |
| Allergic reaction | 5 (9.8) | 1 | 0 | (2.0) |
| Hypertension | 14 (27.5) | 2 | 0 | (3.9) |
| Proteinuria | 14 (27.5) | 0 | – | (0) |
| Hemorrhage | 1 (2.0) | 0 | 0 | (0) |
| Venous thromboembolism | 2 (3.9) | 2 | 0 | (3.9) |
| Nausea | 3 (5.9) | 1 | 0 | (2.0) |
| Vomiting | 4 (7.8) | 0 | 0 | (0) |
| Anorexia | 3 (5.9) | 1 | 0 | (2.0) |
| Ileus | 1 (2.0) | 0 | 1 | (2.0) |
| Diarrhea | 1 (2.0) | 1 | 0 | (2.0) |
| Fatigue | 1 (2.0) | 1 | 0 | (2.0) |

Safety

The main adverse drug reactions of grade 3 or higher in the 51 patients of the safety analysis set were neutropenia 7.8 % (four patients), peripheral neuropathy 3.9 % (two patients), hypertension 3.9 % (two patients), venous thromboembolism 3.9 % (two patients), and allergic reaction 2.0 % (one patient). Grade 4 adverse drug reactions were neutropenia, decreased hemoglobin, and ileus, each 2.0 % (one patient each). In addition, gastrointestinal perforation and clinically significant hemorrhage or proteinuria of grade 3 or higher, which are characteristic of bevacizumab, were not observed (Table 2). Total allergic reactions observed were 9.8 % (5/51 patients), which led to discontinuation of protocol treatment in three cases. Discontinuation of protocol due to peripheral neuropathy occurred in one case.

## Discussion

This trial is the first investigational study of the oxaliplatin stop-and-go concept by a regimen of mFOLFOX7 (intermittent oxaliplatin administration) plus bevacizumab in Japanese patients with unresectable mCRC. This regimen was shown to be clinically useful for Japanese patients, with good tolerability and without impairing treatment efficacy.

Peripheral nerve disorders due to the cumulative toxicity of oxaliplatin are an obstacle to continuing FOLFOX. Therefore, a preplanned withdrawal of oxaliplatin for a period of 8 cycles was set in this study. In order to reduce hematological toxicity, mFOLFOX7 plus bevacizumab without 5-FU bolus administration was used, with bevacizumab co-administered with msLV5FU2 during the oxaliplatin withdrawal period.

Chemotherapy plus bevacizumab is recommended in the guidelines of various countries as the first-line therapy for unresectable mCRC. Comparing the therapeutic effects of different regimens in phase III studies with PFS as the primary endpoint, in the NO16966 study, PFS was 9.4 months in the FOLFOX4 plus bevacizumab group and was 9.3 months in the XELOX plus bevacizumab group [16], while in the HORIZON III study PFS in the mFOLFOX6 plus bevacizumab group was 10.3 months [17]. PFS in this study was 11.8 months, which is comparable to the results of those phase III studies. PFS in the intermittent administration group of the CONcePT trial [13] which preceded this study was 12.0 months, a similar result. Okita et al. [18] conducted mFOLFOX6 (intermittent oxaliplatin administration) plus bevacizumab by the stop-and-go concept with Japanese patients as subjects, and the secondary endpoint PFS was 12.8 months, which is similar to the results of this study.

Preplanned withdrawal of oxaliplatin is one treatment strategy against peripheral neuropathy due to cumulative oxaliplatin toxicity. Peripheral nerve disorders of grade 3 or 4 occurred in 18 % of the FOLFOX4 plus bevacizumab group in the NO16966 study [19] and in 10 % of the mFOLFOX6 plus bevacizumab group in the HORIZON III study [17], but were substantially lower in this study at 3.9 %. Furthermore, peripheral neuropathy of grade 3 or 4 also occurred in 10 % of patients in the intermittent administration groups in the CONcePT trial [13] and in the study

reported by Okita et al. [18]. Therefore, the regimen of this study was very well tolerated by Japanese patients.

With respect to hematological toxicity, the incidence of neutropenia of grade 3 or 4 was 40 % in the FOLFOX4 plus bevacizumab group in the NO16966 study [19] and 24 % in the mFOLFOX6 plus bevacizumab group in the HORIZON III study [17], but was lower in this study at 7.8 %. Okita et al. reported the incidence of neutropenia of grade 3 or 4 to be 40 % [18], indicating that the mFOLFOX7 without bolus 5-FU regimen that we used in our study is good for keeping hematological toxicity low.

There are also some interesting study reports related to continuous oxaliplatin therapy. At the 2012 ASCO Annual Meeting, Yalcin et al. [20] compared a group that received continuous XELOX plus bevacizumab until PD with a group with preplanned withdrawal of oxaliplatin after six courses (18 weeks) of XELOX plus bevacizumab treatment and then continued on maintenance therapy of capecitabine plus bevacizumab. The primary endpoint PFS in the group that continued with capecitabine plus bevacizumab as maintenance therapy was significantly better than PFS in the group that continued with XELOX plus bevacizumab treatment until PD (capecitabine plus bevacizumab maintenance, 11.0 months [95 % CI, 9.1 to 12.9]; continuous XELOX plus bevacizumab, 8.3 months [95 % CI, 7.1 to 9.5] [$P<$ 0.002]). This result suggests the possibility that continued oxaliplatin treatment affects not only tolerability, but also maintenance of effectiveness.

Although the usefulness of the stop-and-go concept for unresectable mCRC is becoming established, including the results of this study, issues still remain from the standpoint of risk/benefit evaluation.

In representative studies of the stop-and-go concept, OPTIMOX1 [11] and OPTIMOX2 [12], oxaliplatin was stopped 12 weeks after the start of treatment, and Yalcin et al. [20] reported stopping oxaliplatin at 18 weeks after the start of treatment, while in this study, as in the CONcePT trial [13], oxaliplatin was stopped at 16 weeks after the start of treatment, and thus there are differences between studies. Because the cumulative maximum therapeutic effect reported by Haller [21] was after about 16 weeks (8 cycles) of FOLFOX4, and the incidence of peripheral neuropathy of grade 3 or higher due to oxaliplatin also increased, a preplanned withdrawal of oxaliplatin after about 16 weeks with the cumulative dose as guide seems to be most effective, but this has not yet been established. A clinical study [22] to resolve this as well as the timing for reintroducing oxaliplatin is currently underway, and we are awaiting the results.

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**Conflict of interest** We declare that we have no conflicts of interest.



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# Induction of a Pathological Complete Response by Four Courses of Neoadjuvant Chemotherapy for Gastric Cancer: Early Results of the Randomized Phase II COMPASS Trial

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## ABSTRACT

**Background.** The prognosis for stage 3 gastric cancer is not satisfactory, even with S-1 adjuvant chemotherapy. A randomized phase II trial was conducted to compare two and four courses of neoadjuvant S-1/cisplatin (SC) and paclitaxel/cisplatin (PC) using a two-by-two factorial design for locally advanced gastric cancer. The primary endpoint was overall survival. We clarified the impact of these regimens on the secondary endpoints, including the clinical and pathological responses, chemotherapy-related toxicities, and surgical results.

**Methods.** Patients received S-1 (80 mg/m$^2$ for 21 days with 1 week's rest)/cisplatin (60 mg/m$^2$ at day 8) or paclitaxel/cisplatin (80 and 25 mg/m$^2$, respectively, on days 1, 8, and 15 with 1 week's rest) as neoadjuvant chemotherapy.

**Results.** Eighty-three patients were assigned to arm A (two courses of SC, $n = 21$), arm B (four courses of SC, $n = 20$), arm C (two courses of PC, $n = 21$), and arm D (four courses of PC, $n = 21$). Pathological response rate was 43 % in arm A, 40 % in arm B, 29 % in arm C, and 38 % in arm D. Pathological complete response was only observed in arms B (10 %) and D (10 %). Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were slightly higher but acceptable in arms B and D. Grade 3/4 surgical morbidities were not commonly observed in all four arms.

**Conclusions.** Pathological complete response could be induced by four courses of neoadjuvant chemotherapy without a marked increase of toxicities, regardless of a SC or PC regimen.

Gastric cancer remains the second leading cause of cancer death worldwide.[1] For locally advanced disease, the standard treatment is chemotherapy and D2 gastrectomy in Asia, D2 plus postoperative chemotherapy with S-1 for 1 year in Japan, and D2 plus postoperative chemotherapy with capecitabine and oxaliplatin for around 6 months in Korea.[2–5] However, even with D2 gastrectomy and

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adjuvant chemotherapy with S-1, the prognosis of stage 3 tumors is not satisfactory.[6] In contrast to the use of adjuvant S-1 chemotherapy for 1 year in Japan, other approaches have been established in Western countries. Pre- and postoperative chemotherapy is a standard treatment in Europe.[7–9] Pre- or postoperative chemoradiation with D2 is frequently selected in the United States.[10]

Combination chemotherapy using S-1 plus cisplatin (SC) is a standard regimen administered for metastatic gastric cancer in Japan.[3,11] However, SC was not tolerable when it was started just after surgery, but was feasible and safe when provided preoperatively.[12–16] Paclitaxel is another key drug used for metastatic disease and has been tested in an adjuvant setting in a phase III trial.[17–19] Moreover, paclitaxel plus cisplatin (PC) demonstrated a high response rate and feasibility for metastatic disease.[17,20] Furthermore, PC achieved a high pathological response rate with acceptable toxicity in the neoadjuvant setting.[21] Both SC and PC are promising regimens for neoadjuvant chemotherapy; however, a suitable duration of treatment has not yet been established. Two courses have been selected in most Japanese studies, while three courses were adopted in the MAGIC phase III trial, which confirmed its survival benefit.[7,14,22] In contrast to neoadjuvant chemotherapy, the patients received S-1 for 1 year or capecitabine plus oxaliplatin for 6 months in the postoperative adjuvant setting after undergoing D2 gastrectomy.[4,5]

On the basis of these previous studies, a randomized phase II trial was conducted to compare neoadjuvant chemotherapy using two and four courses of SC and PC with a two-by-two factorial design for macroscopically resectable locally advanced gastric cancer.[23] The primary endpoint was overall survival (OS). The present study was a randomized phase II trial, which aimed not to draw definite conclusion but to select better regimen and course for the next phase III trial. This report clarified the impact of these regimens on early endpoints, including the clinical and pathological responses, chemotherapy-related toxicities, and surgical results.

## PATIENTS AND METHODS

### *Eligibility Criteria*

The eligibility criteria were as follows: (1) histologically proven gastric adenocarcinoma, (2) T2–3/N+ or T4aN0 in case of scirrhous or junctional tumors, T2–3 with nodal metastasis to the major branched artery, T4aN+ , T4b, paraaortic nodal metastases, or resectable minimal peritoneal metastases confirmed by laparoscopy, (3) no other distant metastasis, (4) age between 20 and 80 years, (5) Eastern Cooperative Oncology Group performance status of 0 or 1, (6) no previous treatment, (7) sufficient organ functions (white blood cell count >4,000/mm$^3$ and <12,000/mm$^3$, neutrophil count >4,000/mm$^3$, hemoglobin >8.0 g/dl, platelet count >100,000/mm$^3$, GOT <100 IU, GPT <100 IU, total bilirubin <1.5 mg/dl, creatinine clearance >30 mg/dl/h according to measured value or Cockcroft–Gault formula, no ischemic change or ventricular arrhythmia by exercise ECG), and (8) written informed consent provided. The exclusion criteria were as follows: (1) serious comorbidities, (2) synchronous or metachronous cancer (synchronous multiple cancers in the stomach included), (3) acute inflammation, (4) systemic treatment with a corticosteroid, (5) hypersensitivity to Cremophor EL, (6) pregnant or breast-feeding women, or women who were contemplating pregnancy, (7) mental disorders, (8) medical history of allergy or hypersensitivity to any drugs, (9) history of alcoholic anaphylaxis, (10) peripheral neuropathy, and (11) patients judged to be inappropriate for the study by the physicians.

The clinical diagnosis of the T and N stages was basically determined by thin-slice CT or multidetector row CT following Habermann's method.[24] Briefly, T4a tumors were defined as transmural tumors with obvious blurring of at least one-third of the tumor extent, or wide reticular strands surrounding the outer border of the tumor. Regional lymph nodes were considered to be involved by metastases if they were larger than 8 mm in the short-axis diameter. Staging laparoscopy was mandatory to diagnose peritoneal metastasis. Our previous study demonstrated that the accuracy was 71.4 % for T staging and 75.9 % for N staging according to the same method and criteria.[25]

### *Preoperative Chemotherapy*

In the SC regimen, S-1 was provided twice a day for a total of 80 mg/m$^2$ for the first 3 weeks of a 4-week cycle, and cisplatin was provided as an intravenous infusion of 60 mg/m$^2$ on day 8 of each cycle, as described previously.[11] In the PC regimen, paclitaxel 60 mg/m$^2$ and cisplatin 25 mg/m$^2$ were administered on days 1, 8, and 15 as one course, which was repeated every 4 weeks.[20] The dose modification criteria were based on the previous studies.[11,21] Neoadjuvant chemotherapy was discontinued if there was documented disease progression, unacceptable toxicity, or withdrawal of consent.

### *Surgery*

During the 2–6 weeks after completion of the neoadjuvant chemotherapy or when the tumors progressed during the treatment, patients proceeded to surgery on the basis of the criteria defined by the protocol. After laparotomy, the resectability was evaluated. Intraperitoneal wash cytology was mandatory. R0 resection was aimed for by gastrectomy with standard D2 lymphadenectomy.[3] D3 dissection or

combined resection of a small part of the peritoneum or adjacent organs were permitted for curative intent. Depending on the location of the primary tumor, the surgeon performed either a total or distal subtotal gastrectomy. In total gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy.

After a macroscopic curative resection was achieved, the patients were strongly recommended to undergo postoperative chemotherapy using S-1 for more than 6 months until 12 months, as long as the tumors did not recur. Any adjuvant treatment other than S-1 was not permitted until a recurrence developed.

### *Registration and Randomization*

Eligible patients were registered into the data center of this study and then randomized as follows: arm A, two courses of SC; arm B, four courses of SC; arm C, two courses of PC; and arm D, four courses of PC. Randomization was performed by a centralized dynamic method using the following factors: scirrhous type including giant type 3 (yes or no), tumor invasion of the esophagus (yes or no), clinical stage 2–3b or 4, creatinine clearance (<60 or ≥60 mg/m$^2$/min), and institution as balancing variables.

### *Study Design and Statistical Methods*

The present study was an open-label, randomized phase II trial of selection design as proposed by Simon.[26] The primary endpoint was the 3-year OS rate. The early key secondary endpoints were the incidence of adverse events, pathological response rate, clinical response rate, and R0 resection rate. The sample size was calculated on the hypothesis that the 3-year OS rate was expected to be between 20 and 40 % for each reference arm of the two courses and SC regimen. When each test arm of four courses and PC regimen achieved 10 % improvement of the 3-year OS rate, the statistical power (selection probability) was calculated to be 0.81, 0.79, and 0.78 for a total sample size of 60, and it was calculated to be 0.85, 0.83, and 0.82 for a total sample size of 80. Considering these calculations, the number of patients to be accrued was set at 60–80 in total.

The progression of tumors was evaluated by the 7th edition of the International Union Against Cancer tumor, node, metastasis classification system.[27] The clinical response was evaluated by the first version of the Response Evaluation Criteria for Solid Tumors.[28] Surgical specimens were pathologically evaluated as grade 0 when there was no degeneration and/or necrosis within the tumor, grade 1a when the area was less than one-third of the tumor, grade 1b when the area was more than one-third and less than two-thirds, grade 2a when the area was more than two-thirds but tumor tissues were apparently remained, grade 2b when only minimal tumor cells remained, and grade 3 when there was no residual tumor.[3] Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). The severity of surgical morbidity was evaluated by the Clavien–Dindo classification.[29]

The protocol was approved by the institutional review boards/ethics committees of each participating institution. This trial was registered in the University Hospital Medical Information Network (UMIN) center (ID UMIN00000 2595).

## RESULTS

### *Patients*

Between October 2009 and July 2011, a total of 83 patients were assigned to arm A (two courses of SC, $n$ = 21), arm B (four courses of SC, $n$ = 20), arm C (two courses of PC, $n$ = 21), and arm D (four courses of PC, $n$ = 21). All patients were eligible and received neoadjuvant chemotherapy. Table 1 shows the patient demographics and tumor characteristics.

The actual courses were defined as one course when cisplatin (CDDP) was provided at least one time during one course. The rate of completion of neoadjuvant chemotherapy was 91 % (19 of 21) in arm A, 60 % (12 of 20) in arm B, 100 % (21 of 21) in arm C, and 81 % (17 of 21) in arm D. The rate of completion of chemotherapy was 76 % (31 of 41) in the SC arm compared to 90 % (38 of 42) in the PC arm, and 95 % (40 of 42) in the two-course arm compared to 71 % (29 of 41) in the four-course arm. A total of six patients did not proceed to surgery because of disease progression. Among the patients who proceeded to surgery, two patients in arm C received a bypass operation because of peritoneal metastasis. Five patients underwent an R2 resection because of peritoneal metastasis, and eight patients had an R1 resection as a result of positive peritoneal cytology. All patients without peritoneal metastasis and positive peritoneal cytology received a D2 gastrectomy. The R0 resection rate was 81 % (17 of 21) in arm A, 75 % (15 of 20) in arm B, 67 % (14 of 21) in arm C, and 76 % (16 of 21) in arm D. The R0 resection rate was 78 % (32 of 41) in the SC arm and 71 % (30 of 42) in the PC arm, while it was 74 % (31 of 42) in the patients treated with two courses and 76 % (31 of 41) in the patients treated with four courses. A flow diagram of the patients is provided in Supplementary Appendix Fig. A1.

**TABLE 1** Patient characteristics

| Characteristic | Variable | Arm A ($n = 21$) | Arm B ($n = 20$) | Arm C ($n = 21$) | Arm D ($n = 21$) |
|---|---|---|---|---|---|
| Age | Median | 66 | 63 | 66 | 67 |
| | Range | 32–79 | 47–76 | 55–80 | 43–77 |
| Gender | M/F | 14/7 | 12/8 | 17/4 | 15/6 |
| Performance status | 0/1 | 21/0 | 20/0 | 20/1 | 20/1 |
| Macroscopic type | Non-scirrhous | 15 | 15 | 15 | 12 |
| | Type 4/giant type 3 | 6 | 5 | 6 | 9 |
| Histological type | Differentiated | 8 | 9 | 11 | 8 |
| | Undifferentiated | 13 | 11 | 10 | 13 |
| Clinical T | T2 | 0 | 0 | 0 | 1 |
| | T3 | 1 | 1 | 2 | 2 |
| | T4a | 17 | 19 | 17 | 15 |
| | T4b | 3 | 0 | 2 | 3 |
| Clinical N | N0 | 1 | 4 | 3 | 4 |
| | N1 | 12 | 7 | 8 | 8 |
| | N2 | 8 | 9 | 9 | 9 |
| | N3 | 0 | 0 | 1 | 0 |
| Clinical M | Negative | 18 | 17 | 17 | 18 |
| | Positive | 3 | 3 | 4 | 4 |
| Site of M | P or CY | 3 | 3 | 3 | 4 |
| | Para-aortic nodes | 0 | 0 | 1 | 0 |

*Response*

Twenty-four patients had only nonmeasurable lesions and 59 had measurable lesions. The overall clinical response, evaluated among all 83 patients, was 43 % (9 of 21) in arm A, 50 % (10 of 20) in arm B, 24 % (5 of 21) in arm C, and 29 % (6 of 21) in arm D (Supplementary Appendix Table A1). The response rate was 46 % (19 of 41) in the SC arm and 26 % (11 of 42) in the PC arm, while it was 33 % (14 of 42) in the patients treated with two courses and 39 % (16 of 41) in those treated with four courses. The non-PD rate was 93 % (38 of 41) in the SC arm and 93 % (39 of 42) in the PC arm, while it was 95 % (39 of 41) in the patients treated with two courses and 90 % (38 of 42) in those treated with four courses.

Table 2 indicates the pathological response of the primary tumor. The pathological response rate, defined as tumor regression by more than two-thirds was 43 % (9 of 21) in arm A, 40 % (8 of 20) in arm B, 29 % (6 of 21) in arm C, and 38 % (8 of 21) in arm D. The pathological response rate was 42 % (17 of 41) in the SC arm and 33 % (14 of 42) in the PC arm, while it was 36 % (15 of 42) in the patients treated with two courses and 39 % (16 of 41) in those treated with four courses. The pathological complete response rate was 0 % (0 of 21) in arm A, 10 % (2 of 20) in arm B, 0 % (0 of 21) in arm C, and 10 % (2 of 21) in arm D. The pathological complete response rate was 0 % with a 95 % confidence interval from 0 to 8 % in the two-course arm and 10 % with a 95 % confidence interval from 3 to 23 % in the four-course arm. The $P$ value for this comparison according to Fisher's exact test was 0.055. All patients who experienced pathological complete response had no tumor cells in either the primary tumor or the lymph nodes dissected. All patients who exhibited a pathological complete response completed four courses of chemotherapy.

*Chemotherapy-Related Toxicities*

The most frequently detected toxicities (all grades) in the SC arm were anemia in 33 patients (81 %), followed by neutropenia in 26 (63 %), appetite loss in 24 (59 %), leukocytopenia in 21 (51 %), fatigue in 15 (37 %), and nausea in 15 (37 %), while those in the PC arm were anemia in 37 patients (88 %), followed by leukocytopenia in 33 (79 %), nausea in 17 (41 %), alopecia in 14 (33 %), anorexia in 16 (38 %), and hyperkalemia in 16 (38 %). Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were slightly higher, but still acceptable, in the four-course arms, regardless of the regimen. Grade 3/4 toxicities were not frequently observed for either the SC or PC regimen. Grade 3/4 nonhematological toxicities occurred in less than 10 % of patients in all arms (Supplementary Appendix Table A2).

**TABLE 2** Pathological response of primary tumor

| Characteristic | Arm A ($n = 21$) | Arm B ($n = 20$) | Arm C ($n = 21$) | Arm D ($n = 21$) |
|---|---|---|---|---|
| Grade 0 | 1 | 5 | 2 | 2 |
| Grade 1a | 10 | 5 | 10 | 9 |
| Grade 1b | 2 | 1 | 2 | 2 |
| Grade 2a | 5 | 3 | 4 | 4 |
| Grade 2b | 2 | 2 | 0 | 0 |
| Grade 3 | 0 | 2 | 0 | 2 |
| Unknown | 0 | 0 | 0 | 0 |
| Unresected | 1 | 2 | 3 | 2 |

*Surgery*

Table 3 shows the details of the surgical procedure performed. Most patients received total gastrectomy and D2 dissection. More than half of the patients who received D2 total gastrectomy received splenectomy. D1 dissection was only selected when the patients had peritoneal metastasis or positive peritoneal cytology.

The surgical morbidity (all grade) is shown in Table 4. Grade 3 morbidities included anastomotic leakage, which occurred in 5 % of the patients in arms A and C, pancreatic fistula, abdominal abscess, and pyothorax, each of which occurred in 5 % of the patients in arm C, and postoperative hemorrhage in 6 % of the patients in arm B. Readmission was observed in one patient from arm C. None of the patients required reoperation. No surgical mortality was observed.

## DISCUSSION

To our knowledge, the present study is the first randomized trial to compare the duration of neoadjuvant chemotherapy for locally advanced gastric cancer. The major finding of this study was that a high pathological complete response rate of 10 % was only achieved when four courses of neoadjuvant chemotherapy were completed. Although the comparison of the pathological complete response did not reach statistical significance, the result was highly suggestive because this trial was a randomized study and there was no bias in the background. So far, such a high pathological complete response rate has never been reported from any other studies using one, two, or three courses of neoadjuvant chemotherapy for gastric cancer.[7,9,14–16,22]

Even though the pathological response was almost equivalent between the two- and four-course arms, as well as between the SC and PC regimens, a pathological complete response was observed only in 10 % of the patients treated with four courses, regardless of the regimen. The

**TABLE 3** Surgical findings

| | Arm A | Arm B | Arm C | Arm D |
|---|---|---|---|---|
| Proceeded to surgery | | | | |
| *n* | 20 | 18 | 20 | 19 |
| Bypass | | | | |
| *n* | 0 | 0 | 2 | 0 |
| Gastrectomy | | | | |
| Total | 15 | 14 | 16 | 13 |
| Distal | 5 | 4 | 2 | 6 |
| Dissection | | | | |
| D1 | 2 | 2 | 2 | 0 |
| D2 | 18 | 16 | 16 | 19 |
| Combined organ resection | | | | |
| Spleen | 9 | 7 | 10 | 11 |
| Gallbladder | 1 | 4 | 4 | 2 |
| Transverse colon | 1 | 0 | 2 | 2 |
| Pancreas | 0 | 0 | 0 | 2 |
| Diaphragm | 0 | 1 | 1 | 0 |
| Liver | 0 | 1 | 0 | 0 |
| Bleeding, g | | | | |
| Median | 365 | 470 | 468 | 320 |
| Range | 60–1280 | 0–1300 | 120–1560 | 70–1990 |
| Time, min | | | | |
| Median | 256 | 239 | 253 | 254 |
| Range | 155–395 | 176–422 | 162–380 | 172–381 |

patients were well randomized to each arm in terms of the background of the patients and tumor characteristics. The compliance with chemotherapy was similar in both the two- and four-course arms. Therefore, an accidental imbalance of patients, tumors, or chemotherapy could not explain the fact that this high pathological complete response was only observed in patients who received four courses of chemotherapy. These results indicated that a pathological complete response was induced by the addition of third and fourth courses. Previously, several investigators reported that the pathological response clearly separated the survival of gastric cancer patients who received neoadjuvant chemotherapy.[30,31] However, it was unclear whether the patients who experienced a pathological complete response had different survival from those who experienced a partial response. Our study will clarify the answer to this question in the future.

In contrast to the pathological response, only one patient (in arm B) exhibited a clinical complete response. A clinical complete response is a rare event in gastric cancer chemotherapy. Previously, a clinical complete response was reported in one of 87 metastatic gastric cancer patients who received SC and also in one of 49 metastatic patients who received a PC regimen.[11,20] The discrepancy between the pathological and clinical responses may be explained

**TABLE 4** Surgical morbidity

| Proceeded to surgery | Arm A | | Arm B | | Arm C | | Arm D | |
|---|---|---|---|---|---|---|---|---|
| | ($n = 20$) | | ($n = 18$) | | ($n = 20$) | | ($n = 19$) | |
| | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 |
| Postoperative bleeding | 2 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| Anastomotic leakage | 1 | 1 | 0 | 0 | 2 | 1 | 0 | 0 |
| Pancreas fistula | 1 | 0 | 3 | 0 | 2 | 1 | 3 | 0 |
| Abdominal abscess | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| Wound infection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ileus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anastomotic stenosis | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Pneumonia | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Pyothorax | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |

by the difficulties in evaluating patients for a clinical complete response. The response of the primary tumor is hard to be evaluated clinically, as the primary tumor is generally a nonmeasurable lesion. In three patients who exhibited a pathological complete response of lymph nodes in this study, the lymph nodes that had been considered to be occupied by the tumor were replaced by connective tissue but were not reduced in size. This is the reason why these three patients were not diagnosed with a clinical complete response of lymph nodes.

The chemotherapy-related toxicities increased when patients were treated with four courses compared to two. Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were more frequently observed in those provided four courses than in those provided two courses of therapy, regardless of the regimen. However, the grade 3/4 toxicities were acceptable in the four-course arms of both regimens. No chemotherapy-related death was observed. On the other hand, surgical morbidities were not frequently observed in all four arms. Moreover, grade 3/4 complications were rare. No surgical mortality was observed. Thus, the administration of four courses of a SC or PC regimen, followed by surgery, appears to be feasible and safe.

Another concern in the four-course arm is the loss of a chance to receive R0 resection as a result of tumor progression during long-term chemotherapy. In the present study, the R0 resection rate was not low in the four-course arm compared with that observed in the two-course arm. Moreover, no patients exhibited disease progression during the third or fourth courses of chemotherapy. Tumor progression was observed during the initial two courses only. Although the rate of completing neoadjuvant chemotherapy was slightly lower in the four-course arm than in the two-course arm, the substantial difference was interpreted to be due to the toxicities observed in a few patients during the third and fourth courses. These results strongly suggest that compliance with chemotherapy was similar between the two- and four-course arms. When comparing the SC and PC regimens as neoadjuvant chemotherapy, both the radiological and pathological response rates were slightly lower in the PC arm than in the SC arm. However, the rates of R0 resection and pathological complete response were almost equivalent. The chemotherapy-related toxicities were feasible and safe in both regimens. The surgical morbidity was also low regardless of the regimen. The long-term survival results of the present study will clarify which regimen is better for neoadjuvant chemotherapy for gastric cancer.

This study included patients with para-aortic nodal metastases or resectable minimal peritoneal metastases. Para-aortic nodal metastasis is classified as M1 but is curable with neoadjuvant chemotherapy and surgery. Two phase II trials of neoadjuvant chemotherapy clarified that a high 3-year survival rate was obtained with neoadjuvant chemotherapy: 27 % with two courses of CPT-11 plus CDDP and 58.8 % with two courses of S-1 plus CDDP.[22,32] On the other hand, a peritoneal lavage cytology positive (CY1) status is also classified as M1 and is also curable with surgery and adjuvant chemotherapy containing S-1. Kodera and coworkers[33] reported that a 2-year survival rate of 46 % was obtained with surgery and S-1 therapy in patients with CY1. Without staging laparoscopy, CY1 or minimally resectable peritoneal metastasis is treated as clinically resectable disease. From the viewpoint of the prognosis and treatment strategy, para-aortic nodal metastases or resectable minimal peritoneal metastases are similar candidates for a trial of neoadjuvant chemotherapy for locally resectable advanced M0 disease.

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ORIGINAL ARTICLE

# Phase II trial of paclitaxel and cisplatin as neoadjuvant chemotherapy for locally advanced gastric cancer

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## Abstract

*Purpose* Paclitaxel–cisplatin (TC) combination is effective and well tolerated in patients with unresectable gastric cancer. We investigated the efficacy and safety of TC for locally advanced gastric cancers in a neoadjuvant setting.

*Methods* Patients received 2–4 courses of paclitaxel (80 mg/m$^2$) and cisplatin (25 mg/m$^2$) on days 1, 8, and 15 in a 4-weekly schedule, followed by radical gastrectomy. Primary endpoint was the pathological response rate: percentage of tumors in which one-third or more parts were affected.

*Results* All 52 patients enrolled were eligible. Thirty-six (69.7 %) patients completed two or more courses of chemotherapy. Forty-three patients (82.7 %) underwent surgery, 33 (63.5 %) had R0 resection, and there was no treatment-related death. The pathological response was 34.6 % (95 % CI 22.0–49.1) for all registered patients; the null hypothesis of tumor response $\leq$10 % was rejected ($p < 0.0001$). The 3-year overall survival was 41.5 % (95 % CI 27.4–55.0).

*Conclusions* The neoadjuvant chemotherapy with TC was safe and effective for patients with locally advanced gastric cancer, and further study is needed to confirm the effectiveness of this regimen.

**Keywords** Cisplatin · Gastric cancer · Neoadjuvant chemotherapy · Paclitaxel · Pathological response

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## Introduction

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer mortality [4]. Surgical eradication of primary tumor and the adjacent lymph nodes represents the best chance for long-term survival [14]; however, poor results of surgery alone for locally advanced disease mandate adjuvant and/or neoadjuvant approaches. A recently published meta-analysis demonstrated a statistically significant benefit of fluorouracil-based adjuvant chemotherapy [11]. Currently, adjuvant chemoradiation with 5-fluorouracil and leucovorin in the USA [9]; perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil in the UK [3]; and postoperative oral fluoropyrimidine (S-1) monotherapy in Japan [13] have each become standards without consensus on the best treatment regimen and the timing. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) showed a significant benefit of S-1 with a hazard ratio for death of 0.68 [13]; however, risk reduction was less in stage IIIA and IIIB than in stage II.

Recently, paclitaxel has emerged as one of the effective drugs for gastric cancer [12]. In the preceding phase II study involving weekly administration of paclitaxel and cisplatin (TC) for patients with unresectable gastric cancer [10], response rate was 41 % and median survival was 10.9 months with acceptable toxicities, despite almost half (24 out of 49) of the patients treated as second-line therapy. The purpose of the present trial was to evaluate the efficacy and safety of neoadjuvant chemotherapy with TC for locally advanced gastric cancers, which may not have been completely resectable without neoadjuvant chemotherapy, or for cases with poor prognostic factors even after curative resection.

## Patients and methods

### Patients

Patients with locally advanced gastric cancer (clinical stage III–IV according to the 1998 classification developed by the Japanese Gastric Cancer Association: JGCA [6]) were enrolled. Eligibility criteria included (1) histologically proven gastric adenocarcinoma, (2) no distant metastasis (M0) other than positive peritoneal cytology (CY1) or resectable peritoneal metastasis adjacent to the stomach (P1) that had no ascites in the upper abdomen, (3) clinical stage IIIB–IV tumors, stage IIIA type 4 or large type 3 ($\geq$8 cm in long axis) tumors, or stage IIIA tumors with esophageal invasion, (4) PS 0 or 1, (5) 20–80 years old, (6) no history of chemotherapy, radiotherapy, or gastric surgery except for gastric bypass, (7) no other active cancer, (8) appropriate organ function, and (9) written informed consent. This phase II trial was approved by the institutional review board of the participating institutions; the UMIN registry number is C000000278.

### Staging

Clinical staging was done by endoscopy, upper gastrointestinal series, and computed tomography (CT) within the 28 days before patient registration. Enhanced spiral or multi-slice CT was performed in 5- to 7-mm slices after patients had consumed more than 400 ml of water to fill the stomach, and tumor (T) and lymph node (N) staging was conducted in median level and window of approximately 60 Hounsfield unit (HU) and 360 HU, respectively. T-staging was defined according to Habermann's criteria [5]. N staging was preformed according to the JGCA classification based on the location of lymph nodes, and N1 and N2 were defined as having a short axis of 8 mm or more and a long axis of 15 mm or more and N3 (paraaortic nodes) as a short axis of 8 mm or more and a long axis of 10 mm or more. Preoperative staging for peritoneal metastasis was confirmed by laparoscopy, including lavage cytology.

### Treatment plan

Patients received paclitaxel (80 mg/m$^2$) and cisplatin (25 mg/m$^2$) on days 1, 8, and 15 of a 4-week regimen; 2–4 courses were prescribed depending on the response to the therapy and resectability of the tumor. If curative resection (R0) was considered possible at 14–20 days after the second course, the patients underwent surgery within 14 days of this determination. In cases where R0 resection was deemed difficult or not likely to succeed after the second course without progressive disease, two additional courses of preoperative chemotherapy were prescribed before attempting surgery. Surgery consisted of gastrectomy with D2 lymphadenectomy. After surgery, patients experiencing a pathological tumor response were prescribed two postoperative courses of the same regimen.

### Evaluation during the protocol treatment

Physical examination and assessment of toxicity were performed prior to each course of chemotherapy. Toxicity was recorded and graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. Abdominal and pelvic CT was performed twice, once after the first course and once after the second course prior to surgery. Preoperative laparoscopy was performed as needed. Clinical response to chemotherapy was evaluated by Response Evaluation Criteria in Solid Tumors

(RECIST) 1.0 based on a central review of CT data. Assessment of pathological response was done centrally by two pathologists and graded according to the proportion of each tumor affected by degeneration or necrosis in the longest cross-sectional surface area of tumor: grade 0, no part; grade 1a, <1/3; grade 1b, ≥1/3 and <2/3; grade 2a, ≥2/3 and <9/10; grade 2b, ≥9/10 and <1; and grade 3, all parts of tumors affected. Pathological response was defined as one-third or more of the tumors affected (grade 1b, 2a, 2b, or 3).

### Endpoints and sample size

The primary endpoint was pathological response rate (pRR) as described above. Forty-five patients were required to confirm a pRR of over 25 %, the threshold pRR was set at 10 % with a one-sided alpha of 0.05 and beta of 0.2, and the sample size was set as 50. The secondary endpoints were 3-year overall survival (OS) rate, curative resection (R0) rate, treatment completion rate, objective response rate of preoperative chemotherapy, and adverse events (AEs).

### Statistical analysis

The primary set used for analysis was all eligible patients. One-sided exact test of the null hypothesis ($H_0$: pRR ≤10 %) based on a binomial distribution was performed in the primary analysis. The 95 % exact (Clopper–Pearson) confidence interval (CI) for the proportion was calculated [2]. The survival curve was estimated using the Kaplan–Meier method; 95 % CIs were calculated with the Greenwood formula. Efficacy and safety monitoring of the treatment were checked every 15 cases based on the Bayesian predictive probability approach. The stopping rule for efficacy was prespecified as a predictive probability of 95 % or more for pRR values below 25 %, and that for safety was a predictive probability of 95 % or more for a serious adverse event rate above 10 %. Statistical analysis was performed with SAS, version 9.2 (SAS Institute, Cary, NC, USA).

## Results

### Patients

Between October 2005 and July 2008, a total of 52 patients were enrolled from nine institutes in Japan, and all patients were eligible. The median age was 65 (range 36–80); male/female ratio, 32/20; and PS 0/1, 45/7. Most tumors were clinically SE or SEI (98 %) and N1 or N2 (87 %), while 15, 6, and 19 % were N3, P1 (resectable), and CY1, respectively (Table 1). Stage grouping was IIIA in 16, IIIB in 15, and IV in 21 patients.

### Preoperative chemotherapy

All 52 patients received preoperative chemotherapy, and 36 (69.7 %) completed 2 or more courses of chemotherapy, including 28, 6, and 2 patients who completed 2, 3, and 4 courses, respectively. The reasons for discontinuation of chemotherapy included progressive disease ($n = 5$, 9.6 %), toxicity ($n = 8$, 15.1 %), patient refusal ($n = 1$, 1.9 %), and others ($n = 1$, 1.9 %). CTC grade 1 and 2 toxicities were observed in 7 (13.5 %) and 25 (48.1 %) patients, and CTC grade 3 or higher hematological and non-hematological toxicities were observed in 18 (32.7 %) and 2 (4.6 %), respectively. There was no treatment-related death (Table 2).

The objective response of chemotherapy was complete response (CR) in 1 (1.9 %), partial response (PR) in 22 (42.3 %), stable disease (SD) in 11 (21.2 %), progressive disease (PD) in 6 (11.5 %), and not evaluable (NE) in 12 (23.1 %) patients, with a response rate of 44.2 % (95 % CI

**Table 1** Patients' profile ($n = 52$)

| Characteristic | Number | % |
|---|---|---|
| Median age, years (range) | 65 (36–80) | |
| Gender | | |
| Female | 20 | 38.5 |
| Male | 32 | 61.5 |
| ECOG performance status | | |
| 0 | 45 | 86.5 |
| 1 | 7 | 13.5 |
| Pretreatment T stage | | |
| T2 (MP, SS) | 1 | 1.9 |
| T3 (SE) | 42 | 80.8 |
| T4 (SEI) | 9 | 17.3 |
| Pretreatment N (location) stage | | |
| N0 | 4 | 7.7 |
| N1 (perigastric) | 20 | 38.5 |
| N2 (peripancreatic) | 20 | 38.5 |
| N3 (para-aortic, etc.) | 8 | 15.3 |
| Pretreatment P, CY, M stage | | |
| P0 | 49 | 94.2 |
| P1 (resectable) | 3 | 5.8 |
| CY0 | 42 | 80.8 |
| CY1 | 10 | 19.2 |
| M0 except P or CY | 52 | 100.0 |
| Histopathology | | |
| Differentiated | 11 | 21.2 |
| Undifferentiated | 41 | 78.8 |

*ECOG* Eastern Cooperative Oncology Group

**Table 2** Grade 3–4 toxicities of neoadjuvant chemotherapy (NCI-CTC, version 3.0)

| Toxicity | Grade 3 | Grade 4 | % Grade 3–4 |
|---|---|---|---|
| Hematological | | | |
| Leukopenia | 3 | 1 | 7.7 |
| Neutropenia | 13 | 1 | 26.7 |
| Anemia | 1 | 0 | 1.9 |
| Thrombocytopenia | 0 | 0 | 0 |
| Non-hematological | | | |
| Allergy | 0 | 0 | 0 |
| Neuropathy | 0 | 0 | 0 |
| Fatigue | 0 | 0 | 0 |
| Anorexia | 0 | 0 | 0 |
| Nausea | 0 | 0 | 0 |
| Vomit | 0 | 0 | 0 |
| Stomatitis | 0 | 0 | 0 |
| Constipation | 0 | 0 | 0 |
| Diarrhea | 0 | 2 | 3.9 |
| Infection | 0 | 2 | 3.9 |
| Syncope | 0 | 1 | 1.9 |

30.5–58.7) for all patients and 57.5 % for patients with measurable disease.

### Operative outcome

A total of 43 patients (82.7 %) underwent surgery, 33 had R0 resection (63.5 %; 95 % CI 49.0–76.4), and 31 patients completed the full protocol treatment. CTC grade 2 or higher complications were observed in 8 patients (18.6 %) and grade 3 or 4 complications in 5 patients (11.6 %), including elevation of alanine transaminase (ALT) and aspartate transaminase (AST) (grades 3 and 4: $n = 1$ for each), low albumin (grade 3: $n = 1$), pneumonia (grade 3: $n = 1$), and infection (grade 3: $n = 1$). One (2.3 %) patient died within 30 days after surgery due to progressive disease.

### Pathological response and survival

The pRR (1b or greater) was observed in 18 cases, which was 41.9 % of the 43 patients who underwent surgery and 34.6 % (95 % CI 22.0–49.1) for all registered patients (Table 3), and the null hypothesis (pRR $\leq$10 %) was rejected ($p < 0.0001$). The pathological stages (TNM, version 6) of patients who underwent surgical resection were classified as follows: stage IA in 3, stage IB in 4, stage II in 3, stage IIIA in 7, stage IIIB in 10, and stage IV in 15. The 3-year OS was 41.5 % (95 % CI 27.4–55.0; Fig. 1). The site of recurrence was peritoneal surface in 11, lymph nodes in 10, liver in two, and other distant metastases in three patients.

## Discussion

In this phase II trial, we tested the TC regimen in neoadjuvant setting especially for clinically advanced gastric cancer. The response rate and the rate of progressive disease of this study were comparable to other studies such as JCOG 0001 [16] with less than 37 % cumulative grade 3–4 toxicities and no morbidity.

The pathological response is among the most reliable surrogates for survival [8]. The pathological response (grade 1b or greater) of JCOG 0001 was 7/55 (12.7 %); however, pathological responses in the MAGIC trial, ACCORD-07, and EORTC 40954 were not reported. Brenner et al. [1] reported on neoadjuvant cisplatin–fluorouracil treatment in patients with M0 gastric cancer; they defined a good pathological response as $\geq$60 % tumor degeneration, and five (15.1 %) good responses were observed among the 33 patients examined. In our study, more than two-thirds of degeneration (2a–3) was observed in 11 (26.1 %) out of 42 patients who underwent resection. We set the primary endpoint as pRR, which was 34.6 %. The mean pRR was 34.6 % among the 52 patients, which was higher than the expected pRR of 25 %, and the lower end of the 95 % CI was 22, which exceeded the threshold pRR of 10 %. Kurokawa et al. evaluated the criteria used to assess tumor response in three neoadjuvant chemotherapy trials of JCOG against upper gastrointestinal cancers; these criteria were RECIST, histological criteria, and Japanese criteria, which include X-ray or endoscopic findings from the primary lesion. In this analysis, differences in response rates between long-term and short-term survivors were compared, and histological response was the best surrogate for OS [8]. In our study, the 3-year survival rate of 41.5 % was better than expected and it might reflect the good pRR.

Since peritoneal spread is the most common pattern of recurrence of gastric cancer, paclitaxel is supposed to be

**Table 3** Pathological response after neoadjuvant chemotherapy

| Grade | No. of tumors | % (95% CI) |
|---|---|---|
| 0 | 9 | 17.7 |
| 1a | 15 | 29.4 |
| 1b | 6 | 11.8 |
| 2a | 7 | 13.7 |
| 2b | 4 | 7.8 |
| 3 | 1 | 2.0 |
| Unresectable | 9 | 17.7 |
| Unknown | 1 | 2.0 |
| 1b–3 | 18 | 34.5 (22.0–49.1) |

Grade 0, no part; grade 1a, <1/3; grade 1b, >1/3 and <2/3; grade 2a, >2/3 and <9/10; grade 2b, >9/10 and <1; and grade 3, all parts of tumors affected (degeneration or necrosis)

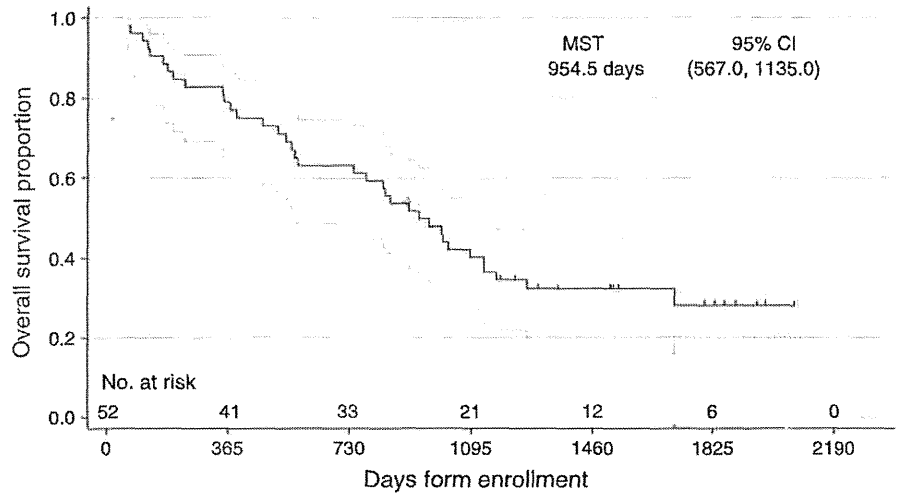


**Fig. 1** Kaplan–Meier plot of overall survival ($n = 52$)

effective for locally advanced gastric cancer [7]. Although in our study peritoneal metastasis was the most frequent cause of recurrence, it was comparable with lymph node recurrence. The effectiveness of paclitaxel should further be tested in randomized trials. Currently, a large phase III trial of adjuvant chemotherapy comparing oral fluorinated pyrimidines with or without sequential paclitaxel has accrued more than 1,480 patients and been followed up [15]. A randomized phase II study comparing 2 or 4 courses of this regimen with 2 or 4 courses of S-1 plus cisplatin as a neoadjuvant therapy is ongoing [17].

In conclusion, the combination of TC was well tolerated and promising as neoadjuvant chemotherapy for patients with locally advanced gastric cancer. Further study is needed to confirm the effectiveness of this regimen.

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**Conflict of interest** All authors declared no conflict of interests.

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# Effect of Daikenchuto (TJ-100) on Postoperative Bowel Motility and on Prevention of Paralytic Ileus after Pancreaticoduodenectomy: A Multicenter, Randomized, Placebo-controlled Phase II Trial (The JAPAN-PD Study)

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We conducted a multicenter, randomized, controlled trial in patients with pancreaticoduodenectomy to investigate the efficacy of Daikenchuto (TJ-100), which is a Kampo medicine (traditional Japanese herbal medicine), for its effect on postoperative bowel motility and for prevention of postoperative paralytic ileus. This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus lasting over 72 h after surgery and (ii) time to having the first postoperative passage of flatus. The secondary endpoints are the incidence of postoperative paralytic ileus in cases that combined with/without enteral alimentation, QOL assessment by the Gastrointestinal Symptom Rating Scale (GSRS) Score (Japanese Version) and visual analogue scale, the change ratio of abdominal circumference, the incidence of postoperative complication, the number of postoperative hospital days, the incidence of surgical site infection and the incidence of postoperative small bowel obstruction within 2 years after surgery. Two hundred and twenty patients are required in the study (110 patients per group).

*Key words: pancreaticoduodenectomy – Japanese herbal medicine (TJ-100) – postoperative paralytic ileus – surgical site infection*

## INTRODUCTION

Pancreaticoduodenectomy (PD) is one of the most extensive surgical procedures with high incidence of morbidity for patients with periampullary disease. Improved surgical skills and modern perioperative care reduced the mortality rate, but there is still a high morbidity rate, which remains about 40–50% (1, 2). In these days, several investigators have reported that a fast-track program reduced the incidence of morbidity and the postoperative hospital days in PD (3, 4). To keep normal state of the digestive function is an essential factor affecting the recovery of postoperative paralytic ileus in the fast-track program. Daikenchuto (TJ-100), which is a traditional Japanese herbal medicine, has been used for the prevention and treatment of postoperative ileus in Japan (5, 6). TJ-100 extract powder (Tsumura & Co., Tokyo, Japan) is manufactured as an aqueous extract containing

2.2% Japanese pepper, 5.6% processed ginger, 3.3% ginseng and 88.9% maltose syrup powder. To date, there has been no prospective study investigating the effect on the normalization of bowel peristalsis after PD. Therefore, we have started a multicenter, randomized, placebo-controlled phase II trial of TJ-100 to evaluate its efficacy for supporting postoperative bowl motility and preventing postoperative paralytic ileus after PD.

## PROTOCOL DIGEST OF THE STUDY

### Objective

Postoperative paralytic ileus after surgery for intraperitoneal organ is one of the common complications (>90% in many series) and recognized as an inevitable response to intraperitoneal surgery (7–9). The JAPAN-PD study is a multicenter, randomized, double-blinded, placebo-controlled, phase II trial, and planned to implement for patients with periampullary tumors (extrahepatic bile duct tumor, tumors of ampulla of Vater and duodenal tumor) and pancreatic tumors (pancreatic cancer, intraductal papillary mucinous neoplasm of the pancreas, pancreatic endocrine tumor and pancreatic neuroendocrine tumor) of the head of pancreas who are expected to undergo PD to investigate an enhancement effect of the bowel motility and the prevention effect of TJ-100 for postoperative paralytic ileus after PD.

### Resources

A research grant from a non-profit organization: epidemiological and clinical Research Information Network (ECRIN).

### Endpoints

This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus lasting over 72 h after surgery and (ii) the time to having the first postoperative passage of flatus. In this study, the postoperative paralytic ileus is defined as the delay of the first postoperative flatus for over 72 h (3.0 days) after surgery (7–9), or the status requires some intervention of treatment for ileus. Every 12 h are counted as 0.5 postoperative day and 24 h as 1.0 postoperative day. The secondary endpoints are the incidence of postoperative paralytic ileus in cases that combined with/without enteral alimentation, QOL assessment by the GSRS Score (Japanese Version) and visual analogue scale about abdominal pain and abdominal distention, the change ratio of abdominal circumference on postoperative day 3 and operative day just after surgery, the incidence of postoperative complication, the number of postoperative hospital days, the incidence of surgical site infection and the incidence of postoperative small bowel obstruction within 2 years after surgery.

### Eligibility Criteria

#### *Inclusion Criteria*

(i) Patients with periampullary tumors (extrahepatic bile duct tumor, tumors of ampulla of Vater and duodenal tumor) and pancreatic tumors (pancreatic cancer, intraductal papillary mucinous neoplasm of the pancreas, pancreatic endocrine tumor and pancreatic neuroendocrine tumor) of the head of the pancreas who are scheduled to undergo PD.
(ii) Age of at least 20 years and older at the time of registration.
(iii) All patients provided written informed consent before initiation of study-related procedures.

#### *Exclusion Criteria*

(i) Clinically problematic cardiac disease.
(ii) Liver cirrhosis or active hepatitis.
(iii) Severe pulmonary disease (interstitial pneumonia, pulmonary fibrosis, pulmonary emphysema etc.).
(iv) Chronic renal failure requiring hemodialysis.
(v) Other malignant disease that can influence the adverse effect.
(vi) Patients with tumors requiring resection of colon.
(vii) Patients who are expected to have severe intra-abdominal adhesion due to past surgical history or past peritonitis history.
(viii) Patients who had used gastrointestinal prokinetic medication, antipsychotic medication or antidepressants.
(ix) Patients who had used Japanese herbal (Kampo) medicines within 4 weeks before registration.
(x) Pregnant or lactating women.
(xi) Any other medical condition that makes the patient unsuitable for including into the study according to the opinion of the investigator.

### Registration

An eligibility report form is sent to the registration center at ECRIN. Eligible patients are centrally randomized to either Arm A (TJ-100) or Arm B (placebo) using primary disease, the presence of preoperative therapy, the presence of pylorus ring in the remnant stomach and the institution as balancing variables. Information regarding the necessary follow-up tests is then sent from the registration center at ECRIN.

### Treatment Methods

#### *ARM A*

In the TJ-100 group, TJ-100 at a dose of 5 g was administered orally as a solution three times daily immediately before meals or every 8 h for 17 consecutive days (15 g/day from preoperative day 3 to postoperative day 14). On the operative day (only once immediately after operation) and

postoperative day 1, TJ-100 were administered as a diluent via enteral feeding tube (10 Fr), which terminates in jejunum to prevent aspiration pneumonia.

*ARM B*

In the placebo group, placebo at a dose of 5 g was administered orally as a solution three times daily immediately before meals or every 8 h for 17 consecutive days (15 g/day from preoperative day 3 to postoperative day 14). On the operative day (only once immediately after operation) and postoperative day 1, placebo were administered as a diluent via enteral feeding tube (10 Fr), which terminates in jejunum to prevent aspiration pneumonia.

### Criteria of Dose Reduction and Discontinuation of the Protocol Treatment

In cases where Grade 2 postoperative diarrhea or other clinical adverse effects (CTCAE version 4.0 criteria) are observed, the patient will be administered reduced dose of the test drug to a dose of 2.5 g, and in case where Grade 3 postoperative diarrhea or other clinical adverse effects (CTCAE version 4.0 criteria) are observed, the protocol treatment will be immediately discontinued.

### Data Collection

Data will be collected prospectively for all patients including history, physical examination, laboratory data, pathologic examination, perioperative clinical information and complications.

### Study Design and Statistical Analysis

This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus for over 72 h after surgery and (ii) the time to have the first postoperative passage of flatus. The multiplicity issue (inflation of the type I error) due to analyzing two endpoints is dealt with using the Bonferroni method. That is, the significance levels for both tests are set at 2.5% to control the overall type I error rate. The sample size was calculated on the basis that the incidence rate of postoperative paralytic ileus for 72 h after surgery was expected to be 90% for the placebo group. In case the effect of reducing the incidence of postoperative paralytic ileus is assumed to be 20% for the TJ-100 group (that is, incidence rate = 70%), the least number of patients to provide the 85% power necessary to confirm the superiority of a group was calculated to be 94 per group for a two-sided 2.5% significance level test. Furthermore, given the number of patients, 84% statistical power is retained to prove the superiority in terms of time to occurrence of postoperative paralytic ileus for the hazard ratio of 0.62. The significance level for this inference is also set at 2.5%. Taking exclusion from analysis of about 15% into account, the number of patients to be accrued was set at 110 per treatment arm (220 in total). The first primary endpoint, incidence rate of postoperative paralytic ileus for 72 h after surgery, will be compared between the two treatment groups using the $\chi^2$ test. The second primary endpoint, time to having the first postoperative passage of flatus, will be analyzed by constructing Kaplan–Meier curves as time-to-event plots. Differences between the curves are tested for significance using log-rank statistics.

## PARTICIPATING INSTITUTIONS

Eleven leading Japanese institutions and hospitals (all of them are high volume center in pancreatic surgery) for PD are participating in this trial.

## Funding

A research grant from a non-profit organization ECRIN.

## Conflict of interest statement

None declared.

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RESEARCH ARTICLE

# Smoking and Associated Factors Among the Population Aged 40-64 in Shahroud, Iran

**Mohammad Shoaib Hamrah[1], Md Harun-Or-Rashid[1], Tomoya Hirosawa[1], Junichi Sakamoto[1], Hassan Hashemi[2], Mohammad Hassan Emamian[3]*, Mohammad Shariati[4], Akbar Fotouhi[5]**

## Abstract

**Background: Smoking is known as a major risk factor for different types of cancer, as well as cardiovascular disease. Its prevalence is increasing in developing countries. The aims of this study were to determine the prevalence of smoking and its associated factors among the population aged 40-64 years in the city of Shahroud which is a representative urban population in Iran. Materials and Methods: A cross-sectional population-based study with stratified random cluster sampling was conducted in 2009 as the first phase of Shahroud Eye Cohort Study. Of 6,311 people, 5,190 participated (82.2%). Information about smoking habit was obtained by face-to-face interview. Results: The overall prevalence of current tobacco smoking was 11.3% (95%CI: 10.5-12.3). It was significantly higher among males than females (25.7% and 0.71%, P<0.001). The prevalence of current cigarette smoking was 10.8% and 1.75% were past smokers. The smoking rate of water-pipe was 0.67%. Unemployed people smoked more than employed (OR=2.66, 95%CI: 1.38-5.14). Conclusions: The prevalence of smoking is low in Shahroud compared with other parts of Iran and other countries. Age, sex, job and marital status were associated with smoking. The low smoking rate among women may be attributed to cultural and social reasons.**

**Keywords:** Prevalence - smoking - tobacco - urban Iran - health survey

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## Introduction

In 2008, Non-Communicable Diseases (NCDs) was account for 63% of a total of 57 million deaths globally. Out of the figure, 36 millions were attributed to cardiovascular diseases, diabetes, cancers and chronic respiratory diseases (WHO, 2011). Smoking is known as one of the main risk factors of cardiovascular diseases (Ezzati et al., 2005; Norum, 2005; WHO, 2011; Eriksen et al., 2012).

World Health Organization (WHO) has estimated that about 6 million people die annually from smoking. If current mortality trends continue, it will rise to more than 8 million deaths per year by 2030 (WHO, 2011b). Such deaths are more prevalence in male (15%) than female (7%) (Al Riyami and Afifi, 2004; Ezzati et al., 2005). Approximately three-quarters of all these deaths will happen in developing countries (Gilbert et al., 2004; Finch et al., 2010).

There are about one billion smokers in the world according to WHO statistics in 2008 (WHO, 2011) Prevalence of smoking is on the rise in many developing countries whereas it has been decreasing in most developed countries (Youssef et al., 2002; Eriksen et al., 2012) Smoking rate in Western Europe decreased by 26% from 1990-2009. On the contrast, cigarette smoking has increased by 57% during the same time in the Middle East and Africa (Eriksen et al., 2012) A recent cohort study showed that the relative risk for death from all causes among current smokers, compared with never smokers, were 2.80 for male smokers and 2.76 for female smokers (Thun et al., 2013).

Several studies were conducted to estimate the prevalence of smoking in Iran (Mohammad et al., 2001; Sarraf-Zadegan et al., 2004; Fotouhi et al., 2009; Meysamie et al., 2010; WHO, 2011; 2011b; 2012; CDC, 2012). According to Iranian National Health and Diseases Survey, the prevalence of smoking has been decreased

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