Table 3 Toxicities

	A: 5-FU→PTX (n = 38)	B: S-1→PTX (n = 40)	C: 5-FU+PTX (n = 39)	D: S-1+PTX (n = 40)
Hematological toxicities				
CTC Grade	>=3	>=3	>=3	>=3
Leucopenia (%)	7.9	7.5	10.3	7.5
Neutropenia (%)	13.2	12.5	25.6	22.5
Thrombocyte (%)	0.0	2.5	0.0	2.5
Hemoglobin (%)	10.5	32.5	10.3	20.0
Total Bil (%)	2.6	2.5	0.0	5.0
Hepatic Tox (%)	7.9	5.0	2.6	7.5
Non-hematological toxicities				
CTC Grade	>=3	>=3	>=3	>=3
Weight loss (%)	2.6	0.0	2.6	0.0
Fatigue (%)	0.0	0.0	0.0	0.0
Lassitude (%)	7.9	12.5	5.1	10.0
Anorexia (%)	10.5	12.5	7.7	10.0
Nausea (%)	2.6	5.0	5.1	2.5
Vomiting (%)	0.0	0.0	2.6	0.0
Stomatitis (%)	5.3	0.0	2.6	2.5
Diarrhea (%)	2.6	2.5	5.1	2.5
Neuropathy (%)	0.0	2.5	5.1	5.0

CTC Common Toxicity Criteria

sequential regimens were 4 (range 1–26) and 3 (range 1–8) in arm A and 6 (range 1–24) and 4 (range 1–30) in arm B, respectively. For the concurrent regimens, these numbers were 6 (range 1–24) and 7.5 (range 1–30) in arms C and D, respectively.

Discussion

The strategy for the chemotherapy of gastric cancer differs from country to country. In Japan, according to community standards, fluoropyrimidine monotherapy has been widely used as the first-line of a sequential strategy, whereas most western countries use doublet or triplet concurrent regimens without second-line treatment. In fact, little is known about whether concurrent regimens or a sequential strategy with satisfactory second- and greater-line treatments would be better. Although one trial has shown the superiority of doublet (S-1 with CDDP) treatment compared with S-1 alone even in Japan [7], other pivotal trials have failed to show the superiority of concurrent regimens [17, 18]. This suggests that sequential strategies may not be so bad if we can use adequate second- (and more)-line therapies in sequence. Thus, when we decided to evaluate PTX in a clinical trial, we created the study plan so as to evaluate whether PTX should be used in second-line (sequential) or in first-line (concurrent) treatment.

In accordance with the general rule in a randomized phase-II trial, in the present study we assumed that we should choose the best regimen in the aspect of 10-month overall survival (OS). However, as shown in the results, all four arms showed good survival times with very small differences. This finding suggests that the difference between concurrent and sequential strategies may be very small if we take enough care with the timing of regimen changes and are meticulous in surveying for clinical disease progression. Similar trends have been observed with some other malignancies; breast cancer is one of the examples. Several studies have been conducted to show the survival superiority of concurrent regimens, but superiority was seen only in TTF and the response rate (RR) [19, 20]. As a result, the sequential strategy is still used. Recently, the result of the GEST trial in pancreatic cancer showed a superior RR and a superior TTF in the combination arm. Despite this superiority, this concurrent strategy also failed to improve OS [21]. Our phase-II trial with its small sample size nevertheless suggests that the sequential strategy could be considered for the treatment of gastric cancer, along with other types of cancer, and that the sequential use of S-1 followed by paclitaxel (PTX) remains as an alternative for patients who are for some reason not indicated for the S-1/CDDP combination.

One more issue to be evaluated in our trial was the difference between infusional 5-FU and oral S-1. The results of a worldwide advanced gastric cancer trial (FLAGS trial) comparing S-1 plus CDDP (SF) versus 5-FU plus CDDP (CF) failed to show a superior effect of SF over CF [22]. The JCOG9912 trial has already shown no

inferiority of S-1 compared to infusional 5-FU in the first-line setting [6]. However, that trial did not limit the post-treatment, so the setting of PTX use in first- or second line mandatorily might show different results. The present study had started before the results of these two trials were disclosed. Consequently, it is important to check whether our results are in line with the data obtained in the JCOG9912 and the FLAGS trials. In our study, the OS, PFS, and RR for the 5-FU-containing and S-1-containing regimens were almost the same, without any significant differences, suggesting both oral and infusional fluorinated pyrimidine regimens have similar potency, a finding which would be confirmatory of the previous trials. In general, treatment with an oral agent would be more preferable both for the patients and for medical staff than a treatment requiring continuous intravenous infusion, with its risks of infection and thrombotic events.

In conclusion, our study did not show sufficient prolongation of survival with a concurrent strategy to proceed to a phase-III trial; however, the sequential arms showed survival comparable to that in the concurrent arms, with a lower incidence of neutropenia. In patients who are ineligible for CDDP, sequential treatment starting from S-1 and proceeding to PTX would be a good alternative strategy, considering the quality of life (QOL) and cost-benefits of an oral agent as first-line treatment.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
2. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjödén PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol. 1997;8:163–8.
3. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer. 1993;72:37–41.
4. Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer. 1995;71:587–91.
5. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol. 2003;21:54–9.
6. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10:1063–9.
7. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
8. Sakamoto J, Matsui T, Kodera Y. Paclitaxel chemotherapy for the treatment of gastric cancer. Gastric Cancer. 2009;12:69–78.
9. Ajani JA, Fairweather J, Dumas P, Patt YZ, Pazdur R, Mansfield PF. Phase II study of Taxol in patients with advanced gastric carcinoma. Cancer J Sci Am. 1998;4:269–74.
10. Murad AM, Petroianu A, Guimaraes RC, Aragao BC, Cabral LO, Scalabrini-Neto AO. Phase II trial of the combination of paclitaxel and 5-fluorouracil in the treatment of advanced gastric cancer: a novel, safe, and effective regimen. Am J Clin Oncol. 1999;22:580–6.
11. Ninomiya M, Kondo K, Matsuo K, Hirabayashi N, Kojima H, Kobayashi M, et al. Multicenter phase II trial of combination chemotherapy with weekly paclitaxel and 5-fluorouracil, for the treatment of advanced or recurrent gastric carcinoma. J Chemother. 2007;19:444–50.
12. Ueda Y, Yamagishi H, Ichikawa D, Okamoto K, Otsuji E, Morii J, et al. Multicenter phase II study of weekly paclitaxel plus S-1 combination chemotherapy in patients with advanced gastric cancer. Gastric Cancer. 2010;13:149–54.
13. Morita S, Baba H, Tsuburaya A, Takiuchi H, Matsui T, Maehara Y, et al. A randomized phase II selection trial in patients with advanced/recurrent gastric cancer: Trial for Advanced Stomach Cancer (TASC). Jpn J Clin Oncol. 2007;37:469–72.
14. Kaplan EL, Meier P. Nonparametric estimation form incomplete observations. J Am Stat Assoc. 1958;53:457–81.
15. Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall; 1984.
16. Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Rep. 1985;69:1375–81.
17. Narahara H, Iishi H, Imamura H, Tsuburaya A, Chin K, Imamoto H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer. 2011;14:72–80.
18. Kim YH, Koizumi W, Lee KH, Kishimoto T, Chung HC, Hara T, et al. Randomized phase III study of S-1 alone versus S-1 + docetaxel in the treatment for advanced gastric cancer (The START trial). J Clin Oncol. 2011;29 (4s; ASCO Gastrointestinal Cancers Symposium Abstract 7).
19. Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky EK, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 2003;21:588–92.
20. Miller KD, McCaskill-Stevens W, Sisk J, Loesch DM, Monaco F, Seshadri R, et al. Combination versus sequential doxorubicin and docetaxel as primary chemotherapy for breast cancer: a randomized pilot trial of the Hoosier Oncology Group. J Clin Oncol. 1999;17:3033–7.
21. Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Fukutomi A, Sugimori K,et al. Randomized phase III study of gemcitabine plus S-1 (GS) versus S-1 versus gemcitabine (GEM) in unresectable advanced pancreatic cancer (PC) in Japan and Taiwan: GEST study. J Clin Oncol. 2011;29 (15s; ASCO Annual Meeting Abstract 4007).
22. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28:1547–53.

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ORIGINAL ARTICLE

Phase II study of FOLFOX4 with "wait and go" strategy as first-line treatment for metastatic colorectal cancer

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Abstract
Purpose To evaluate the efficacy and safety of FOLFOX4 using "wait and go" strategy in treating metastatic colorectal cancer.
Methods The conventional FOLFOX4 was repeated every 2 weeks. We waited until the recovery of symptoms from persistent neurotoxicity within an added period of 2 weeks, before performing the next cycle ("wait and go" strategy).
Results We enrolled 58 patients, in whom a total of 481 cycles were administered (median 8 per patient; range 1–16). Toxicity was evaluated in 58 patients and response in 55. The major toxic effect was grade 3/4 neutropenia (33%). Painful paresthesia or persistent functional impairment was observed in 4 patients (7%). The response rate was 40% (95% confidence interval; 27.1–52.9%). The median progression-free survival time was 10.2 months, the 1-year survival rate was 89%, and the median overall survival time was 27.6 months.
Conclusions These findings indicate that this "wait and go" strategy reduces the frequency of persistent neuropathy while maintaining efficacy against metastatic colorectal cancer.

Keywords FOLFOX · Neuropathy · Metastatic colorectal cancer · Oxaliplatin · "Wait and go"

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Background

Oxaliplatin, a third-generation platinum anticancer drug, has been shown to be effective for the treatment of metastatic colorectal cancer (CRC) [1, 5, 9, 21]. Currently, the FOLFOX chemotherapy regimen, consisting of oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (LV), has become the standard regimen as first-line treatment for metastatic colorectal cancer [5, 9, 21]. The European adjuvant trial for colon cancer (MOSAIC) demonstrated significant improvement in 3-year disease-free survival when oxaliplatin was added to infusional 5-FU and LV [1].

One of the well-known dose-limiting factors of oxaliplatin is a delayed-onset, cumulative, dose-related peripheral neuropathy, characterized by persistent paresthesias affecting the hands and feet, and which does not remit between cycles of treatment [5, 18]. Persistent peripheral neuropathy with pain or function impairment interfering with activities of daily living (grade 3) occurs in 10–20% of patients receiving total oxaliplatin doses >750–850 mg/m^2 [5, 9, 21]. Of great concern is the development of persistent peripheral neuropathy that requires complete discontinuation of oxaliplatin, regardless of its efficacy, to avoid a debilitating neuropathy, which may take 6–10 months to resolve [5, 7]. Although this neuropathy is largely reversible, safety data from the MOSAIC trial determined that at 4 years, a small minority of patients (<5%) have grade 3 persistent peripheral neuropathy after 6 months of adjuvant FOLFOX4 treatment [2]. Various schedules have been pursued to reduce neuropathy. A randomized trial of FOLFOX4 versus scheduled intermittent oxaliplatin (OPTIMOX 1) was associated with a slight reduction in grade 3 neuropathy (17.9% versus 13.3%, $P = 0.12$) without lack of efficacy in response or progression-free survival [22]. Despite equivalent efficacy, the OPTIMOX 1 "stop and go" strategy has not been widely adopted for all patients. This is probably as a result of variability in management of patients by different physicians, heterogeneity of the disease, and inability to reinstitute oxaliplatin at the time of progression, often because of persistent neuropathy [7].

For patients with unresectable metastatic disease, the duration of treatment is indefinite, extending until disease progression or until the treatment is no longer tolerated. Hence, it is imperative to manage appropriately the persistent peripheral neuropathy, which causes deteriorating in the quality of life during treatment. No single strategy, including calcium (Ca)–magnesium (Mg) supplementation [8, 11, 12] and various antineuropathic and antiepileptic medications [4, 10], has proven effective for preventing or reducing the cumulative neuropathy associated with oxaliplatin.

One possible approach to prevent grade 3 sensory neurotoxicity during treatment is to wait for the complete recovery of paresthesia or dysesthesia from persistent neurotoxicity until 29 days, followed by the subsequent course without dose modification. If paresthesia or dysesthesia continues over 29 days, the dose of oxaliplatin is reduced in the subsequent course, to maintain the antitumor effect of FOLFOX. We conducted the present phase II study to investigate this novel "wait and go" strategy.

Methods

The eligibility criteria for inclusion onto the study were as follows: adenocarcinoma of the colon or rectum; unresectable metastases; at least one measurable lesion of 1 cm or a residual nonmeasurable lesion; adequate bone marrow (hemoglobin >9.0 g/dl, leukocyte count lower limits of normal −12,000/mm^3, neutrophils <1,500/mm^3, platelet count 100,000/mm^3), liver (AST and ALT 2.5 upper limits of normal [UNL], total bilirubin 1.5 UNL, alkaline phosphatases 2.5 UNL), and renal function (creatinine less than UNL); Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; and age 20–80 years. Previous adjuvant fluoropyrimidine chemotherapy, if given, must have been completed at least 2 weeks before inclusion. Patients with uncontrolled infection, massive ascites or pleural effusion, brain metastases, second malignancies, bowel obstruction, current watery diarrhea, a history of oxaliplatin-based adjuvant chemotherapy, or disease confined to previous radiation fields were excluded. Written informed consent was required and the Ethical Committee approved the study.

Chemotherapy

Eligible patients were treated with the FOLFOX4 regimen [1, 9, 21]. Each cycle comprised oxaliplatin 85 mg/m^2 and l-LV 100 mg/m^2 intravenously (IV) administered simultaneously for 2 h followed by 5-FU 400 mg/m^2 IV bolus followed by 5-FU 600 mg/m^2 infusion for 22 h on day 1, and the same therapy, without the oxaliplatin, administered on day 2 (total 46 h after the initial 2 h IV) of a 14-day treatment cycle. Pretreatment with a 5-hydroxytryptamine-3 antagonist and dexamethasone was strongly recommended, although the administration of intravenous calcium and magnesium was not permitted in order to prevent oxaliplatin-induced neuropathy. Treatment was continued until disease progression (PD), unacceptable toxicity, or patient choice.

Toxicity was assessed before starting each 2-week cycle using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0. A specific scale was used for sensory neurotoxicity: grade 1 is brief paresthesia with complete regression before the next cycle, grade 2 is persistent paresthesia or dysesthesia without functional impairment over the next cycle, and grade 3 is painful paresthesia or persistent functional impairment (Table 1).

Table 1 Specific scale for sensory neurotoxicity

Grade	Sensory neurotoxicity
1	Brief paresthesia with complete regression before the next cycle (<15 days)
2	Persistent paresthesia or dysesthesia without functional impairment over the next cycle (≧15 days)
3	Painful paresthesia or persistent functional impairment

Chemotherapy was delayed until recovery if neutrophils <1,500/mm^3, platelets <75,000/mm^3, or for significant persistent non-hematological toxicity. If grade 4 neutropenia, grade 3/4 thrombocytopenia, or grade 3/4 gastrointestinal toxicities occurred, the FU dose was reduced to 300 mg/m^2 for the bolus component and 500 mg/m^2 for the infusion component and the oxaliplatin dose was reduced to 65 mg/m^2. In the case of grade 2 paresthesia at a new cycle of treatment, the next cycle of FOLFOX4 was delayed until the recovery of paresthesia from persistent neurotoxicity for up to 2 additional weeks (<29 days). If it persisted for 29 days, the oxaliplatin was reduced to 65 mg/m^2. If grade 3 paresthesia was present during treatment, oxaliplatin was omitted from the regimen.

Treatment was discontinued if subsequent reduction was indicated.

Evaluation

Pretreatment evaluation included complete patient histories, physical examinations, complete blood cell counts, biochemistry involving liver and renal functions, urinalysis, tumor markers including CEA and CA19-9, chest roentgenogram, electrocardiogram, and computed tomographic scans of the abdomen and chest. According to NCI-CTC version 3.0, toxicity and laboratory variables in complete blood cell counts, biochemistry, and urinalysis were assessed weekly during the first course, on days 1 and 15 from the second through to the sixth course and at least once during subsequent courses. CT scans were repeated to evaluate lesions every two courses and tumor markers were measured at the same time. Responses were evaluated according to the RECIST criteria [20]. To confirm partial response (PR) (30% or greater decrease in the sum of the longest dimensions of target lesions, referenced against the baseline sum of the longest dimensions of target lesions together with stabilization or decrease in size of nontarget lesions) or complete response (CR) (disappearance of all target and nontarget lesions together with normalization of tumor marker levels), tumor measurements were repeated no less than 4 weeks after objective response was firstly obtained. Responses were assessed by external review. Overall survival (OS) was defined as the time from treatment initiation to death from any cause. Progression-free survival (PFS) was the time from treatment initiation to first documentation of disease progression detected by the external review or death from any cause (censored at second-line chemotherapy). Time-to-treatment failure (TTF) was the time from treatment initiation to discontinuation of treatment, first documentation of disease progression by the external review, or death from any cause.

Statistical evaluations

The phase II study was designed to test the null hypothesis that the true response probability is less than the clinically significant level of 25%. The response rate of first-line FOLFOX was reported to be from 45 to 50%. The alternative hypothesis of the response rate in this study was >45%, because the "wait and go" strategy to prevent grade 3 paresthesia might diminish the response. The probability of accepting treatment with a response probability (25%) was $P = 0.05$. The probability of rejecting treatment with a response rate of 45% was $P = 0.2$; therefore, the required number of patients was estimated to be 49. Allowing for a patient ineligibility rate of about 20%, we planned to enroll 60 patients. The 95% confidence interval (CI) was calculated for the RR, PFS, and TTF. OS, PFS, and TTF were calculated by the Kaplan–Meier method.

Results

Patients' characteristics

We enrolled 58 patients between March 2006 and April 2008, all of whom met all eligibility requirements and received at least one course of treatment. Patient characteristics are summarized in Table 2, and all patients were evaluated for toxicity and response. The median age of patients was 67.5 years (range, 37–80 years); 48 patients had an ECOG PS of 0 and 10 patients had an ECOG PS of 1. There were 13 patients with advanced disease with primary tumors and 45 patients in recurrent status. Primary sites were the colon in 35 patients and the rectum in 23 patients. Metastatic sites were in the liver in 39 patients, lungs in 17, lymph nodes in 21, and peritoneum in 11.

Safety

All 58 patients enrolled in the phase II study were assessable for safety and received 481 treatment courses (median, 8 courses; range, 1–16 courses). The median relative dose intensity was 76.9% for oxaliplatin, 76.7% for bolus FU, and 77.8% for infusion FU. The causes of treatment discontinua-

Table 2 Patients' profile ($n = 58$)

Characteristic	No. of patients %
Median age, years (range)	67.5 (37–80)
Sex	
Male	36
Female	22
ECOG PS	
0	48
1	10
2	0
Disease status	
Advanced	3
Recurrent	45
Primary tumor	
Colon	35
Rectum	23
Differentiation	
Well	11
Moderate	42
Poor	5
Metastatic sites	
Liver	39
Lymph node	21
Lung	17
Peritoneum	11
Others	4
No. of metastatic sites	
0	0
1	25
>1	33

tion were disease progression in 20 patients (34.5%), delayed recovery from toxicity such as neutropenia, thrombocytopenia, and liver dysfunction in 6 patients, withdrawal of consent, mainly due to economic issues, in eight cases, surgery for metastases in five patients, allergic reaction in five patients, subsequent reduction in four patients, and grade 3 paresthesia in four patients (6.9%). There were no serious unexpected adverse events and no treatment-related deaths.

The overall incidences (%) of hematological and non-hematological toxicities in the phase II study are listed in Table 3. Grade 3/4 neutropenia was the most common adverse event and occurred in 32.8% of all 58 patients. No patient had febrile neutropenia. With the exception of paresthesia, major non-hematological toxicities were liver dysfunction, anorexia, stomatitis, and diarrhea. Grade 3 non-hematological toxicities were diarrhea (1.7%) and nausea (1.7%). We observed grade 1 paresthesia in 24 patients (41.4%), grade 2 in 13 patients (22.4%), and grade 3 in four patients (6.9%). Cumulative incidence of paresthesia is shown in Fig. 1. The median times to onset of

Table 3 Observed adverse events according to number of patients

Event	Number of patients ($n = 58$)				
	NCI-CTC grade, version 3				
	1	2	3	4	3/4, %
Leucopenia	10	28	6	0	10.3
Neutropenia	0	9	9	10	32.8
Anemia	12	14	1	0	1.7
Thrombocytopenia	28	6	2	0	3.4
Anorexia	12	9	0	0	0
Nausea	15	6	0	0	0
Vomiting	6	2	0	0	0
Fatigue	12	6	0	0	0
Diarrhea	4	2	1	0	1.7
Constipation	1	0	0	0	0
Stomatitis	4	0	0	0	0
Abnormal AST	27	5	1	0	1.7
Abnormal ALT	17	4	0	0	0
Hyperbilirubinemia	7	1	0	0	0
Neuropathy[a]	24	13	4	–	6.9

[a] A specific scale was used for neuropathy (Table 1)

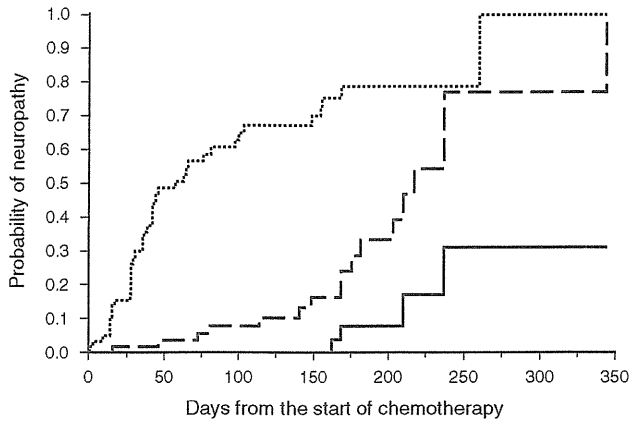

Fig. 1 Cumulative incidence of neuropathy. *Solid line*, grade 3 neuropathy ($n = 4$); *broken line*, grade 2 neuropathy ($n = 13$); *dotted line*, grade 1 neuropathy ($n = 24$)

paresthesias were 54.5 days for grade 1 and 213.5 days for grade 2, respectively. Grade 3 paresthesia was observed from 162 to 237 days from the start of chemotherapy. The median cumulative doses of oxaliplatin associated with paresthesia were 255 mg/m^2 for grade 1,764 mg/m^2 for grade 2, and 973 mg/m^2 for grade 3.

The dose reductions were required in 16 of all 58 patients (27.6%). Among these 16 patients, the reasons for dose reduction were grade 4 neutropenia in eight patients, grade 3/4 gastrointestinal toxicities in one patient, grade 3/4 thrombocytopenia in three patients, and grade 2 paresthesia in only one patient. The treatment delay within 2 weeks was observed in 50 of all 58 patients (86.2%) among 171 of

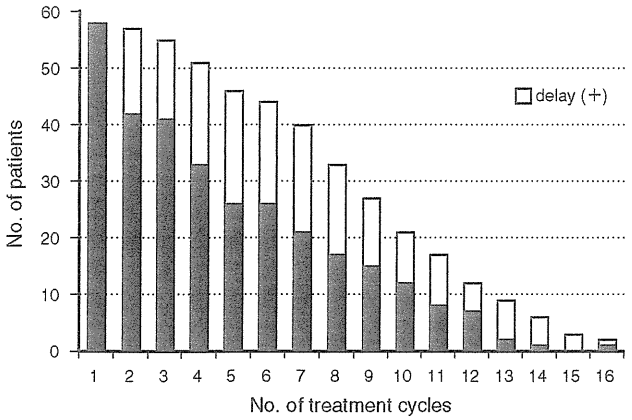

Fig. 2 The frequency of treatment delays in terms of treatment cycle. *Black bar*, numbers of patients who started the treatment within 29 days from the initial day of the previous chemotherapy cycle; *White bar*, numbers of patients who started the treatment over 29 days from the initial day of the previous chemotherapy cycle

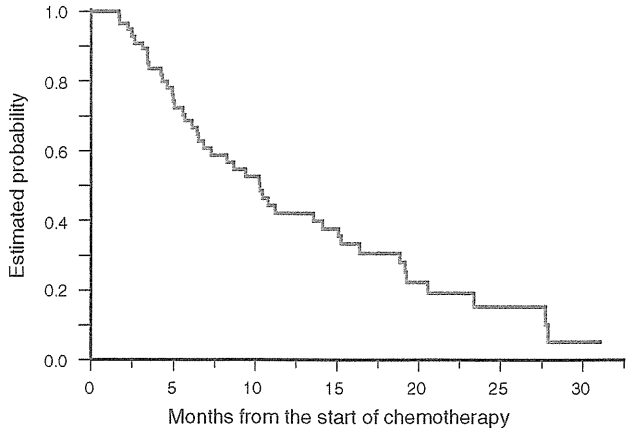

Fig. 3 Kaplan–Meier estimates of progression-free survival ($n = 58$)

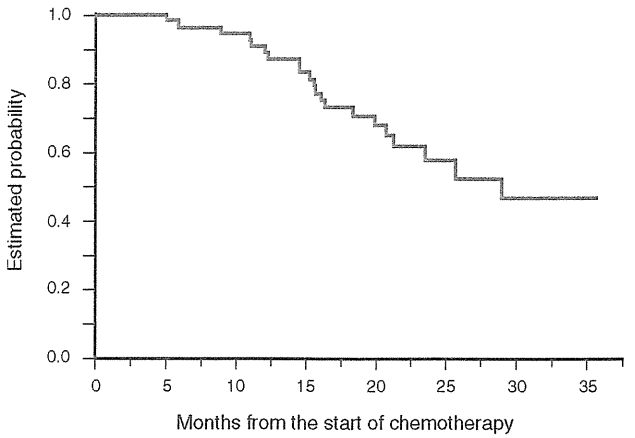

Fig. 4 Kaplan–Meyer estimates of overall survival ($n = 58$)

all 481 treatment courses (35.6%). The frequency of treatment delay over 2 weeks was from 40.9 to 100% after the fourth treatment course (Fig. 2).

Efficacy

The response was assessed as CR, PR, stable disease (SD) (less than a 30% reduction and less than a 20% increase in the sum of the longest dimensions of target lesions, referenced against the baseline sum of the longest dimensions of target lesions together with stabilization or decrease in size of nontarget lesions), and progressive disease (PD) in 2, 20, 25, and 8, respectively, of the 55 patients in the efficacy analysis set (three were not assessable). The RR was 40.0% (95% CI 28.1–53.2%) and the disease control rate (CR + PR + SD) was 85.5% (95% CI 73.8–92.4%).

The median follow-up period was 15.5 months as of the data cut-off date, October 15, 2009. The median PFS was 10.2 months (95% CI 6.4–14.0 months) (Fig. 3), median overall survival time (MST) was 27.6 months (95% CI 20.6–35.6 months) (Fig. 4), and median TTF was 5.0 months (95% CI 3.6–5.1 months). The patients who received the second-line chemotherapy or the surgery for metastases without PD were censored at the date of image examination immediately before the second-line chemotherapy or the surgery for metastases in PFS analysis. The 1- and 2-year survival rate of MST was 89.0% (95% CI 80.7–97.3%) and 57.8% (95% CI 42.3–73.4%), respectively. Of the 58 patients, 46 (79.3%) discontinued treatment and received second-line chemotherapy.

Discussion

We set out to determine whether the "wait and go" strategy for FOLFOX4 in the treatment of metastatic colorectal cancer would be effective. This is the first study of FOLFOX4 with the novel "wait and go" strategy, which minimizes painful paresthesia or persistent functional impairment during treatment by a 2-week wait for the recovery of paresthesia or dysesthesia from persistent neurotoxicity at the new cycle of treatment. Using this strategy, a very promising efficacy, low incidence of painful paresthesia or persistent functional impairment of 6.9% was obtained in our phase II study: an RR of 40.0%, a median PFS of 10.2 months, and an MST of 27.6 months with a 1-year survival rate of 89.0%. Our efficacy results are comparable to those of other recently reported FOLFOX4 regimens for metastatic colorectal cancer, although the RR of 40.0% is slightly lower than previously reported rates of 45% [9] to 49.5% [5]. One possible explanation might be that the frequency of treatment delay of up to 2 weeks in almost 40% of cases in the fourth and fifth treatment course might diminish the confirmation rate of response (Fig. 2). However, it is true that the RR of 40.0% with 95% CI from 28.1 to 53.2% met the primary endpoint of this study.

In this study, the allowance for a patient ineligibility rate was set at 20%, which is twice the ordinary rate of 10%, because the aim of this study was to evaluate the new "wait and go" strategy concept. Fortunately, all 58 accrued patients were treated with this strategy. During this study, the new molecular targeting drug, bevacizumab, was approved at April 2007 by the Japanese regulatory authorities, and the combination of bevacizumab and chemotherapy including the FOLFOX4 regimen became one of the standard therapies for metastatic colorectal cancer in Japan. The introduction of bevacizumab to clinical practice slowed patient accrual in this trail. At 2 years from the start of this study, the number of enrolled patients reached 58 patients, which was more than the required 49 patients initially estimated as necessary for statistical evaluation of this trial. We halted accrual of patients in April 2008 in accordance with the recommendation of the safety monitoring committee.

The grading system, originally developed by Levi and co-workers [16], takes into account both intensity and duration of symptom-related oxaliplatin-induced neurological toxicity. At present, the most commonly used neurological toxicity scale is the NCI-CTC, which considers only the intensity of neuropathy. Our grading system used in this study was consistent with that by Levi et al. [16, 17], in terms of the consideration of both intensity and duration of symptom-related oxaliplatin-induced neurological toxicity. The duration reported by Levi et al. was within 1 week or 2 weeks [16, 17]. Because the new cycle of FOLFOX4 is begun every 2 weeks, we decided on 2 weeks as an appropriate period to evaluate grade 1 or 2 paresthesia. However, the criteria for grade 3 neurological toxicity (painful paresthesia or persistent functional impairment) used in our study are similar to that of the NCI-CTC. Thus, our criteria are appropriate to indirectly compare the frequency of grade 3 neurological toxicity between other clinical trials and this trial.

The frequency of grade 3 neurological toxicity was 6.9% in this trial. In a European trial in advanced colorectal cancer, 18% of patients assigned to the FOLFOX4 regimen had grade 3 neurosensory toxicity during treatment [5]. The same rate was observed among patients assigned to the FOLFOX4 regimen in a North Central Cancer Treatment Group study in metastatic colorectal cancer [9]. In the Multicenter International Study of Oxaliplatin/5-Fluorouracil, Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC), 12.4% of patients treated with FOLFOX4 developed grade 3 paresthesia during therapy [1]. The rates of grade 3 neurotoxicity in those studies are higher than the 6.9% observed in this study. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 study, the incidence of grade 3 neurotoxicity was reported to be 8.4% among patients treated with the FLOX regimen (500 mg/m^2 FU intravenous (IV) bolus weekly for 6 weeks plus 500 mg/m^2 LV IV weekly for 6 weeks with 85 mg/m^2 oxaliplatin IV administered on weeks 1, 3, and 5 of each 8-week cycle for three cycles [13, 14]). This lower incidence of grade 3 neurological toxicity was speculated to be partly due to the scheduled rest in the FLOX regimen. The 2-week wait in the FOLFOX4 regimen depending on the persistency of neurological toxicity might prevent grade 3 neurological toxicity, even in metastatic disease.

The dose reduction and discontinuation of oxaliplatin due to neurological toxicity has varied in different trials. Rothenberg et al. reported the 85 mg/m^2 oxaliplatin in FOLFOX4 was reduced to 65 mg/m^2 in cases of persistent paresthesia or dysesthesia with preserved function, but not activities of daily living (grade 2), or temporary (7–14 days) paresthesia or dysesthesia with pain or function impairment that interferes with activities of daily living (grade 3) [18]. Oxaliplatin was omitted from the regimen until recovery in the case of grade 2 persistent paresthesia or dysesthesia, or grade 3 temporary (1–14 days) paresthesia or dysesthesia. The incidence of grade 3 cumulative neuropathy is reported to be 3%. This lower incidence might be explained by the 6 cycles as the median number of treatment cycles, due to the second-line setting for progressive colorectal cancer after the irinotecan-containing regimen. In the study on first-line FOLFOX reported by de Gramount et al. [5], oxaliplatin was reduced in cases of persistent ($\geq$14 days) paresthesia or temporary (7–14 days) painful paresthesia or temporary functional impairment. In cases of persistent ($\geq$14 days) painful paresthesia or persistent functional impairment, oxaliplatin was omitted from the regimen until recovery. Paresthesia with pain and cumulative paresthesia interfering with function occurred in 10.5 and 16.3% of patients, respectively. The dose intensity was 76% for FU and 73% for oxaliplatin during all cycles, which is similar to the 76.7% for bolus FU and 77.8% for infusion FU and 76.9% for oxaliplatin in our study. Considering the similar dose intensity of oxaliplatin, the "wait and go" strategy might effectively prevent painful paresthesia or persistent functional impairment compared with previously reported conventional methods to reduce the dose and to discontinue oxaliplatin.

Our data have some limitations. First, our results were obtained in a single-armed phase II study including small number of patients. Additionally, FOLFOX4 was used without molecular targeting drugs such as bevacizumab [19] or anti-human epidermal growth factor receptor monoclonal antibodies [3, 6]. The independent studies are warranted to extrapolate this "wait and go" strategy to molecular targeting drug-containing regimens. Second, the primary endpoint in this trial was the RR, not the reduction in neurotoxicity. Prospective phase III trials, including larger numbers of patients, are needed to corroborate our

results. However, we believe that our results suggest that this "wait and go" strategy could be a treatment of choice for patients who are reluctant to encounter persistent neurological toxicity, especially in the palliative setting, with or without molecular targeting drugs. Third, we evaluated the neurological toxicity based on clinicians' reports. In 2006, the FDA recommended that patient-reported outcomes should be considered the gold standard in addition to physician observation. Written in layman language, patient-reported outcomes have been advocated by the NCI since 2006 alongside NCI-CTC. Patients' assessment tools should be used for greater accuracy of interpretation of patient-reported outcomes [15, 23].

In conclusion, the "wait and go" strategy may be effective to prevent painful paresthesia or persistent functional impairment during treatment while maintaining the efficacy of the FOLFOX4 regimen for metastatic colorectal cancer. Further evaluation is needed to examine whether this strategy can be compared with the "stop and go" strategy [22].

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Conflict of interest No authors have any conflict of interest.

Appendix

The following investigators participated in the study: Mitsugu Kochi, Ken Hagiwara (Nihon University School of Medicine, Tokyo, Japan); Yuki Tanabe (Asahikawa Medical University, Hokkaido, Japan); Eiji Meguro, Akinori Takagane, Makoto Kobayashi (Hakodate Goryokaku Hospital, Hokkaido, Japan); Hiroyuki Shibata, Kou Miura (Tohoku University, Miyagi, Japan); Masayuki Sato (Miyagi Cancer Center, Miyagi, Japan);, Yutaka Hoshino, Fumihiko Osuka (Fukushima Medical University, Fukushima, Japan); Michitaka Nagase (Jichi Medical University, Tochigi, Japan); Miki Adachi (IUHW Mita Hospital, Tokyo, Japan); Kenji Katsumata (Tokyo Medical University, Tokyo, Japan); Masanori Yoshino (Nippon Medical School Musashi Kosugi Hospital, Kanagawa, Japan); Reiji Aotake, Koji Doi (Fukui Red Cross Hospital, Fukui, Japan); and Takuji Fukui (Midori Municipal Hospital, Aichi, Japan).

References

1. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343–2351. doi:10.1056/NEJMoa032709
2. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27:3109–3116. doi:10.1200/JCO.2008.20.6771
3. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 27:663–671. doi:10.1200/JCO.2008.20.8397
4. Cassidy J, Bjarnason G, Hickish T, Topham C, Provencio G, Bodoky G, Landherr L, Koralewski P, Lopez-Vivanco G, Said G (2006) Randomized double blind (DB) placebo (Plcb) controlled phase III study assessing the efficacy of xaliproden (X) in reducing the cumulative peripheral sensory neuropathy (PSN) induced by oxaliplatin (Ox) and 5-FU/LV combination (FOLFOX4) in first line treatment of patients (pts) with metastatic colorectal cancer (MCRC). J Clin Oncol 24(Suppl):18S (Abstr 3507)
5. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
6. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocakova I, Ruff P, Blasinska-Morawiec M, Smakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J (2010) Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 28:4697–4705. doi:10.1200/JCO.2009.27.4860
7. Eng C (2009) Toxic effects and their management: daily clinical challenges in the treatment of colorectal cancer. Nat Rev Clin Oncol 6:207–218. doi:10.1038/nrclinonc.2009.16
8. Gamelin L, Boisdron-Celle M, Morel A, Poirier AL, Berger V, Gamelin E, Tournigand C, de Gramont A (2008) Oxaliplatin-related neurotoxicity: interest of calcium-magnesium infusion and no impact on its efficacy. J Clin Oncol 26:1188–1189; author reply 1189–1190. doi:10.1200/JCO.2007.15.3767
9. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23–30. doi:10.1200/JCO.2004.09.046
10. Grothey A (2005) Clinical management of oxaliplatin-associated neurotoxicity. Clin Colorectal Cancer 5(Suppl 1):S38–S46
11. Grothey A, Nikcevich D, Sloan J, Kugler J, Silberstein P, Dentchev T, Wender D, Novotny P, Chitaley U, Alberts S, Loprinzi C (2010) Intravenous calcium and magnesium For oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7J Clin Oncol published online on December 28, 2010. doi:10.1200/JCO.2010.1231.5911

12. Hochster HS, Grothey A, Childs BH (2007) Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. J Clin Oncol 25:4028–4029. doi:10.1200/JCO.2007.13.5251
13. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, Petrelli NJ, Findlay MP, Seay TE, Atkins JN, Zapas JL, Goodwin JW, Fehrenbacher L, Ramanathan RK, Conley BA, Flynn PJ, Soori G, Colman LK, Levine EA, Lanier KS, Wolmark N (2007) Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 25:2198–2204. doi:10.1200/JCO.2006.08.2974
14. Land SR, Kopec JA, Cecchini RS, Ganz PA, Wieand HS, Colangelo LH, Murphy K, Kuebler JP, Seay TE, Needles BM, Bearden JD III, Colman LK, Lanier KS, Pajon ER Jr, Cella D, Smith RE, O'Connell MJ, Costantino JP, Wolmark N (2007) Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. J Clin Oncol 25:2205–2211. doi:10.1200/JCO.2006.08.6652
15. Leonard GD, Wright MA, Quinn MG, Fioravanti S, Harold N, Schuler B, Thomas RR, Grem JL (2005) Survey of oxaliplatin-associated neurotoxicity using an interview-based questionnaire in patients with metastatic colorectal cancer. BMC Cancer 5:116. doi:10.1186/1471-2407-5-116
16. Levi F, Misset JL, Brienza S, Adam R, Metzger G, Itzakhi M, Caussanel JP, Kunstlinger F, Lecouturier S, Descorps-Declere A et al (1992) A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid, and oxaliplatin using an ambulatory multichannel programmable pump. High antitumor effectiveness against metastatic colorectal cancer. Cancer 69:893–900
17. Levi FA, Zidani R, Vannetzel JM, Perpoint B, Focan C, Faggiuolo R, Chollet P, Garufi C, Itzhaki M, Dogliotti L et al (1994) Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. J Natl Cancer Inst 86:1608–1617
18. Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, Hart LL, Gupta S, Garay CA, Burger BG, Le Bail N, Haller DG (2003) Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 21:2059–2069. doi:10.1200/JCO.2003.11.126
19. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzen F, Cassidy J (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 26:2013–2019. doi:10.1200/JCO.2007.14.9930
20. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
21. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229–237. doi:10.1200/JCO.2004.05.113
22. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, Andre T, Tabah-Fisch I, de Gramont A (2006) OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer-a GERCOR study. J Clin Oncol 24:394–400. doi:10.1200/JCO.2005.03.0106
23. Trotti A, Colevas AD, Setser A, Basch E (2007) Patient-reported outcomes and the evolution of adverse event reporting in oncology. J Clin Oncol 25:5121–5127. doi:10.1200/JCO.2007.12.4784

Pharmacokinetics of Oxaliplatin in Gastrointestinal Cancer Patients with Malignant Ascites

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Summary

The pharmacokinetics of oxaliplatin in plasma and ascitic fluid was investigated in 5 gastrointestinal cancer patients with malignant ascites. Oxaliplatin was administered at 85 mg/m^2 by 2-hour infusion in the FOLFOX4 regimen, and the concentrations of total and free platinum were measured. There was a trend of lower plasma C_{max} values of total platinum in patients with a larger volume of ascitic fluid. The AUC_{0-t} values of mean concentration curves of total plasma platinum, total ascites platinum, free plasma platinum, and free ascites platinum were 31.15, 7.96, 4.93 and 2.93 μg·h/mL, respectively. The concentrations of free ascites platinum were similar to those of free plasma platinum at the last sampling time of 26 h in each patient. The decrease or disappearance of ascitic fluid was observed in 4 patients. These results suggest that oxaliplatin exerted a beneficial effect in gastrointestinal cancer patients with malignant ascites, even when administered intravenously.

Key words: **Gastrointestinal cancer, ascites, oxaliplatin, FOLFOX4, pharmacokinetics.**

INTRODUCTION

The peritoneal dissemination of gastrointestinal cancer occurs mainly as a direct invasion of cancer cells [1]. It is more common in advanced gastric cancer and causes many serious complications including massive ascitic fluid, resulting in the poor prognosis of the patient [2]. For the treatment of malignant ascites, the antitumor activity and pharmacokinetics of intraperitoneal administration of cisplatin have been studied [3,4]. However, its usefulness still remains unclear. Oxaliplatin is a third-generation platinum consisting of the diaminocyclohexane carrier ligand and the leaving group of oxalate. Its antitumor spectrum in tumor models differs from that of cisplatin [5,6]. The combination treatment of oxaliplatin with leucovorin (LV) plus 5-fluorouracil (FU), designated as FOLFOX4 regimen, has been widely used for the first- and second-line therapy of metastatic colorectal cancer [7-9]. The effectiveness of such combination therapies including FOLFOX4 has also been reported against gastric cancers in phase II or III studies [10-13]. Oxaliplatin has also been used for the treatment of colorectal peritoneal carcinomas by intraperitoneal administration [14,15]. Recently the modified FOLFOX4 regimen was reported to be effective against gastric cancer patients with malignant ascites [16]. However, as far as we know, no clinical studies have been conducted to investigate the pharmacokinetics of oxaliplatin administered systemically in patients with malignant ascites. This study was planned to investigate the pharmacokinetics of oxaliplatin in both plasma and malignant ascitic fluid. Furthermore, the efficacy of the FOLFOX4 treatment was preliminarily examined against measurable lesion and ascites.

PATIENTS AND METHODS

This study was carried out in accordance with the Declaration of Helsinki, as amended in Edinburgh, Scotland, October 2000, and the good clinical practice. The study protocol was approved by the Institutional Review Board of Nihon University School of Medicine.

Inclusion criteria and study design: This study was a prospective and open clinical trial. The primary objective was to investigate the pharmacokinetics of oxaliplatin in both plasma and malignant ascites. Furthermore, the efficacy of FOLFOX4 treatment was preliminarily examined against measurable lesion and ascites. The inclusion criteria were: (1) histologically proven, unresectable gastrointestinal cancer with malignant ascites; (2) age 20-74 years old; (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; (4) adequate organ functions defined as white blood cell count of 4-12 x 10^9/L, platelet count ≥100 x 10^9/L, serum transaminase (aspartate aminotransferase and alanine aminotransferase) levels ≤100 U, serum bilirubin level ≤1.5 mg/dL and serum creatinine ≤ upper limit of normal range; (5) no prior FOLFOX chemotherapy; (6) no other severe medical conditions; and (7) provision of written informed consent.

Treatment and sample collection: FOLFOX4 consisted of 2-h infusion of oxaliplatin, 85 mg/m^2 in 250 ml of 5% dextrose solution and *l*-LV 100 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and 22-h infusion of 5-FU 600 mg/m^2 on Day 1, and the same therapy without oxaliplatin on Day 2, and this was repeated every 2 weeks. A drain was implanted in the peritoneum of patients for the collection of ascitic fluid prior to FOLFOX4 treatment. The volume of ascitic fluid was estimated by applying the method reported for automated hepatic volumetry for living related liver transplantation [17]. Briefly, an experienced radiologist manually traced the contours of ascitic fluid on a Digital Imaging and Communications in Medicine viewer. The circumscribed areas were then multiplied by the CT section thickness. In Patient No.1, blood and ascitic fluid were collected at pre-dose, 15, 60 min, 2, 2.3, 2.75, 3.0 and 4.0 h after the initiation of the first oxaliplatin administration. In other patients, they were collected at pre-dose, 60 min, 2.0, 2.3, 4.0, 6.0 and 26 h similarly. Samples were collected into a heparinized tube at a volume of 8 mL at each sampling time, centrifuged at 1,050 × g for 10 min at 4°C, and 1 mL of each supernatant was stored at -20°C. The remaining samples were used for the ultrafiltration to measure free platinum concentration. Namely

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the plasma and ascites samples were centrifuged at 1,050 × g for 30 min at 4°C by using the Amicon MPSI micropartition system with YMT membranes (30,000 MW cut-off) [18]. The supernatant was stored at -20°C.

Drug assay: The platinum concentration of plasma, plasma ultrafiltrate, ascitic fluid, and ascitic fluid ultrafiltrate kept at -20°C was determined by flameless atomic absorption spectrophotometric analysis according to the method previously described [19]. The lower limit of quantification of platinum was 25 ng/mL for plasma ultrafiltrate, ascitic fluid, and ascitic fluid ultrafiltrate, and 100 ng/mL for plasma.

Pharmacokinetic parameters: Peak concentration (C_{max}) and time to reach peak concentration (T_{max}) were recorded directly from plasma/ascites concentration-time data. Area under the plasma/ascites concentration-time curve between 0 h and the last sampling time (AUC_{0-t}) was calculated by the linear trapezoidal method by using Microsoft Excel software.

Safety and efficacy: The adverse events were graded using the National Cancer Institute Common Toxicity Criteria version 3. The response of measurable and assessable disease sites was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.

RESULTS

From July 2006 to April 2009, FOLFOX4 was administered to a total of 5 patients, 2 with gastric cancer and 3 with colorectal cancer, who had malignant ascites. The patient demographics and characteristics are shown in *Table 1*. The patients consisted of 3 men and 2 women, with a median age of 58 years (range: 50-65 years). The median body surface area was 1.54 m^2 (range: 1.22-1.73 m^2), and the median dose of oxaliplatin was 134 mg/body/day (range: 100-150 mg).

Pharmacokinetics of oxaliplatin

Plasma and ascites concentrations of oxaliplatin in each patient are shown in *Figure 1*. From the results obtained in Patient N. 1, the last sampling time of 4 h measured was indicated to be not enough. Therefore, in Patients N. 2-5, the last sampling time was extended to 26 h. The mean plasma and ascites concentration curves of oxaliplatin in these patients are shown in *Figure 2*. The pharmacokinetic parameters of C_{max} and T_{max}, which are expressed as actual values observed in each patient or in a mean concentration curve, and AUC_{0-t} are shown in *Table 2*. There was a trend of lower plasma C_{max} values of total platinum in patients with a larger volume of ascitic fluid (Patients N. 1 and 2). The C_{max} values of the mean concentration curve and their ranges in the 5 patients of total plasma platinum, total ascites platinum, free plasma platinum, and free ascites platinum were 2.74 (1.10-2.95), 0.31 (0.18-0.51), 0.52 (0.25-1.37) and 0.12 (0.11-0.20) μg/mL, respectively. The T_{max} values of ascites platinum concentration were later than those of plasma platinum concentration. Among 4 patients excluding Patient N. 1, the AUC_{0-t} values of the mean concentration curve and their ranges of total plasma platinum, total ascites platinum, free plasma platinum, and free ascites platinum were 31.15 (18.30-37.31), 7.96 (5.43-10.44), 4.93 (3.58-6.33) and 2.93 (2.38-3.54) μg•h/mL, respectively. Although the difference in total platinum C_{max} values between plasma and ascites was considerable, that of free platinum AUC_{0-t} values was less than C_{max} values. This may be associated with the similar concentration of free platinum between plasma and ascites at the last sampling time (26 h) in each patient.

Clinical effect

In Patients N. 2, 3 and 5, malignant ascites decreased clearly and disappeared after 1 to 4 cycles of FOLFOX4 treatment (*Table 3*). The treatment was continued up to 10 to 17 cycles. According to RECIST, a partial response was observed in Patients N. 2, 3 and 5, stable disease in Patient N. 4, and progression disease in Patient N. 1.

Four adverse events were observed; one grade-3 neutropenia in Patient N. 4, one grade-2 nausea/vomiting in Patient N. 3, one grade-2 diarrhea and one grade-1 neuropathy in Patient N. 1. These were not critical and could be managed easily.

DISCUSSION

The recently modified FOLFOX4 regimen with 85 mg/m^2 of oxaliplatin has been reported to be effective against gastric cancer patients with malignant ascites [16]. Forty-eight patients with malignant ascites were enrolled in this study, and 22 patients (45.8%) received mFOLFOX4 therapy as first-line treatment. The disappearance or improvement of ascites was seen in 17 patients (35.4%). However, the pharmacokinetics of oxaliplatin in patients with malignant ascites remains undetermined.

The results of our study show that FOLFOX4 can be given safely to gastrointestinal cancer patients with malignant ascites. Although the total platinum C_{max} values of ascites are considerably lower than those of plasma (0.31 vs 2.74 μg/mL by mean value), the free platinum AUC_{0-t} values of ascites are close to those of plasma (2.93 vs 4.93 μg•h/mL by mean value) (*Table 2*). This may be associated with the similar concentration of free

TABLE 1 - *Patient demographics and characteristics*

Clinical features	Patient number No. 1	No. 2	No. 3	No. 4	No. 5
Gender	Male	Female	Female	Male	Male
Age (Year)	50	65	55	62	58
Cancers	Colorectal	Colorectal	Gastric	Gastric	Colorectal
Previous operation	Stoma	No	No	Stoma	No
Histological type Differentiation	Moderately	Moderately	Poorly	Poorly	Moderately
Organ involvement					
Lymph node	+	+	−	−	+
Liver	+	−	−	−	−
Skin	−	−	+	−	−
Prior chemotherapy	S-1+CPT-11	None	S-1+Docetaxel	S-1+Docetaxel	None
Ascites (mL)	5396	4856	340	1469	3299

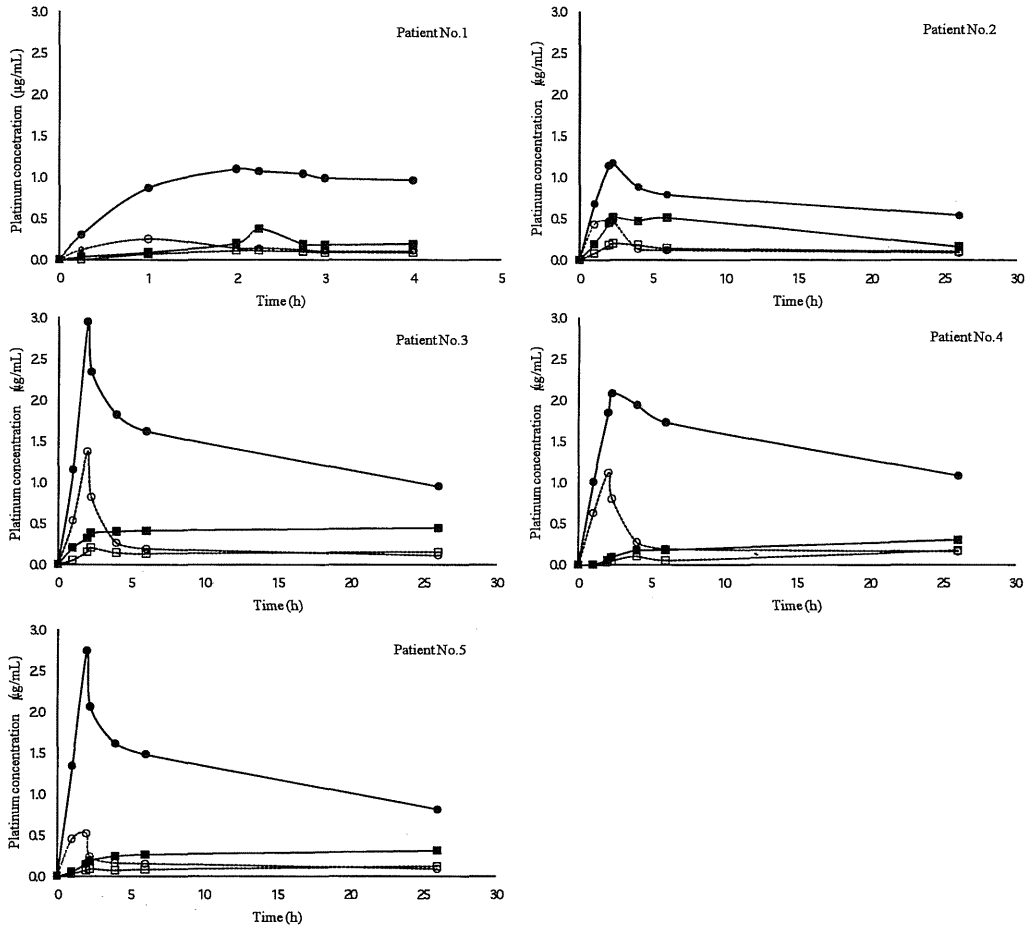

FIGURE 1 - Plasma and ascites concentration of platinum in each patient. Total platinum in plasma (filled circles, solid line), free platinum in plasma (open circles, dotted line), total platinum in ascites (filled squares, solid line), and free platinum in ascites (open squares, dotted line).

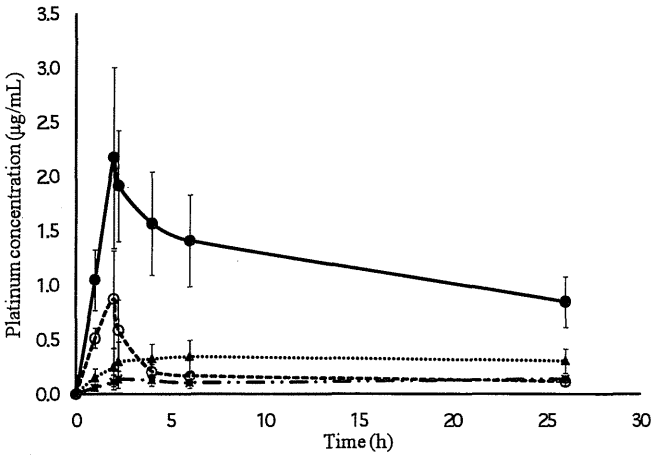

FIGURE 2 - Mean plasma and ascites concentration of platinum in Patients 2-5. Total platinum in plasma (filled circles, solid line), free platinum in plasma (open circles, dotted line), total platinum in ascites (filled squares, solid line), and free platinum in ascites (open squares, dotted line). Bars show the standard deviation.

platinum between plasma and ascites at the last sampling time (26 h) in each patient (*Figure 1*). Such a profile of free platinum concentration in both plasma and ascites after oxaliplatin administration may have resulted in its antitumor activity against malignant ascites (*Table 3*). Of the 5 patients enrolled, the ascitic fluid disappeared in 3 patients and decreased in 1 patient. It is speculated that oxaliplatin transferred from the plasma to the abdominal cavity after the intravenous administration and persisted in ascites. Then the ascites oxaliplatin concentration reached an equilibrium state with the plasma concentration, and oxaliplatin exerted an antitumor activity against peritoneal cancer cells.

Although the last sampling time in our study was 26 h, it was reported that free plasma platinum was detected even 21 days after the oxaliplatin administration of 130 mg/m^2 [20]. Furthermore, it was reported that the terminal half-life of free platinum after the oxaliplatin administration was long and its distribution volume was large [21]. Although the free platinum concentration detected by our method might include platinum bound to low molecular weight proteins or peptides [20,21], these pharmacokinetic profiles of oxaliplatin may be associated with its antitumor activity observed in our study. While it would have been ideal to investigate the pharmacokinetic profile of oxaliplatin in the plasma and ascitic fluid over a longer period, we limited the last sampling time to 26 h in this study to avoid the excessive burden caused by sampling procedure on the patients.

There was a trend of lower plasma C_{max} values of total platinum in patients with a larger volume of ascites (*Tables 1 and 2*). The volumes of ascitic fluid in Patients N. 1 and 2 were 5396 and 4856 mL, and the total plasma platinum C_{max} values were 1.10 and 1.17 μg/mL, respectively. On the other hand, the volumes of ascetic fluid in Patients N. 3 and 4 were 340 and 1469 mL, and the total plasma platinum C_{max} values were 2.95 and 2.08 μg/mL, respectively. Although the difference of C_{max} values between Patients N. 1/2 and 3/4 is not marked, it is noteworthy that the volume of ascitic fluid may affect the pharmacokinetics of oxaliplatin in plasma after FOLFOX4 treatment.

TABLE 2 - *Pharmacokinetic parameters of each patient and mean concentration.*

Patient Samples number		Total platinum			Ultrafiltrated platinum		
		C_{max} (μg/mL)	T_{max} (h)	AUC_{0-t} (μg•h/mL)	C_{max} (μg/mL)	T_{max} (h)	AUC_{0-t} (μg•h/mL)
1	Plasma	1.10	2.0	3.49	0.25	1.0	0.58
	Ascites	0.37	2.3	0.64	0.11	2.0/2.3*	0.31
2	Plasma	1.17	2.0	18.30	0.47	2.0/2.3*	3.58
	Ascites	0.51	2.3/6.0*	9.07	0.20	2.3	3.27
3	Plasma	2.95	2.0	36.07	1.37	2.0	5.88
	Ascites	0.44	26	10.44	0.15	2.0/26*	3.54
4	Plasma	2.08	2.3	37.31	1.12	2.0	6.33
	Ascites	0.18	6.0	5.43	0.17	26	2.50
5	Plasma	2.74	2.0	32.51	0.52	2.0	3.87
	Ascites	0.31	26	6.74	0.12	26	2.38
Mean	Plasma	2.74	2.0	31.15	0.52	2.0	4.93
	Ascites	0.31	26	7.96	0.12	26	2.93

T_{max} and C_{max} are actual values. AUC_{0-t} was calculated as described in "PATIENTS AND METHODS". Mean pharmacokinetic parameters were calculated from mean concentration data of Patients No. 2-5 in *Figure 2*. * The same C_{max} value was observed at two time-points.

TABLE 3 - *Antitumor activity.*

Site of tumor	Response	N. (%)	Patient N.
Ascites	Disappeared	3 (60)	2, 3, 5
	Decreased	1 (20)	4
	No change	1 (20)	1
	Increased	0	–
Measurable lesion	CR	0 (0)	–
	PR	3 (60)	2, 3, 5
	SD	1 (20)	4
	PD	0 (0)	1

CONCLUSION

The AUC_{0-t} values of free platinum in the ascitic fluid were relatively similar to those in the plasma in patients with gastrointestinal cancers treated with the FOLFOX4 regimen. The decrease in ascitic fluid was observed in 4 of 5 patients, suggesting that oxaliplatin exerts a beneficial effect in gastrointestinal cancer patients with malignant ascites. Further study is required to confirm the efficacy and safety of FOLFOX4 treatment in this patient population.

REFERENCES

[1] Dupont JB Jr., Lee JR, Burton GR, Cohn I Jr. Adenocarcinoma of the stomach: review of 1497 cases. Cancer. 1978; 41(3): 941-7.

[2] Kakeji Y, Maehara Y, Tomoda M, Kabashima A, Ohmori M, Oda S, et al. Long term survival of patients with stage IV gastric carcinoma. Cancer. 1998; 82(12): 2307-11.

[3] Kochi M, Fujii M, Takano S, Kato Y, Kawakami T, Kanamori N, et al. Pharmacokinetic study of intraperitoneal cisplatin chemotherapy for gastric cancer as an adjuvant setting. Jpn J Cancer Chemother. 1995; 22(11): 1535-7.

[4] Terashima M, Ikeda K, Takagane A, Sasaki N, Abe K, Araya M, et al. Pharmacokinetic analysis of low-dose intraperitoneal cis-platinum administration. Jpn J Cancer Chemother. 1998; 25(9) : 1433-5.

[5] Raymond E, Buquet-Fagot C, Djelloul S, Mester J, Cvitkovic E, Allain P, et al. Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. Anti-Cancer Drugs. 1997; 8(9): 876-85.

[6] Woynarowski JM, Chapman WG, Napier C, Herzig MCS, Juniewicz P. Sequence- and region- specificity of oxaliplatin adducts in naked and cellular DNA. Mol Pharmacol. 1998; 54(5): 770-7.

[7] de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000; 18(16): 2938-47.

[8] Goldberg RM, Sargent DJ, Morton RF, Morton RF, Fuchs CS, Ramanathan RK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004; 22(1): 23-30.

[9] Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. J Clin Oncol. 2003; 21(11): 2059-69.

[10] De Vita F, Orditura M, Matano E, Bianco R, Carlomagno C, Infusino S, et al. A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (FOLFOX-4) as first-line treatment of advanced gastric cancer patients. Br J Cancer. 2005; 92(9): 1644-9.

[11] Louvet C, Andre T, Tigaud JM, Gamelin E, Douillard JY, Brunet R, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol. 2002; 20(23): 4543-8.

[12] Kim DY, Kim JH, Lee S-H, Kim TY, Heo DS, Bang Y-J, et al. Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Ann Oncol. 2003; 14(3): 383-7.

[13] Al-Batran S-E, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008; 26(9): 1435-42.

[14] Elias D, Sideris L, Pocard M, Ede C, Ben Hassouna D, Ducreux M, et al. Efficacy of intraperitoneal chemohyperthermia with oxaliplatin in colorectal peritoneal carcinomatosis. Preliminary results in 24 patients. Ann Oncol. 2004; 15(5): 781-5.

[15] Elias D, Benizri E, DiPietrantonio D, Menegon P, Malka D, Raynard B. Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. Ann Surg Oncol. 2007; 14(2): 509-14.

[16] Oh SY, Kwon H-C, Lee S, Lee DM, Yoo HS, Kim S-H, et al. A phase II study of oxaliplatin with low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) for gastric cancer patients with malignant ascites. Jpn J Clin Oncol. 2007; 37(12): 930-5.

[17] Nakayama Y, Li Q, Katsuragawa S, Ikeda R, Hiai Y, Awai, K, et al. Automated hepatic volumetry for living related liver transplantation at multisection CT. Radiology 2006; 240(3): 743-8.

[18] Vermorken JB, van der Vijgh WJF, Klein I, Hart AAM, Gall HE, Pinedo HM. Pharmacokinetics of free and total platinum species after short-term infusion of cisplatin. Cancer Treat Rep. 1984; 68(3): 505-13.

[19] LeRoy AF, Wehling ML, Sponseller HL, Friauf WS, Solomon RE, Dedrick RL. Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. Biochem Med. 1977; 18(2): 184-91.

[20] Gamelin E, Le Bouil A, Boisdron-Celle M, Turcant A, Delva R, Cailleux A, et al. Cumulative pharmacokinetic study of oxaliplatin, administered every three weeks, combined with 5-fluorouracil in colorectal cancer patients. Clin Cancer Res. 1997; 3(6): 891-9.

[21] Lévi F, Metzger G, Massari C, Milano G. Oxaliplatin: pharmacokinetics and chronopharmacological aspects. Clin Pharmacokinet. 2000; 38(1): 1-21.

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ORIGINAL REPORT

Five-Year Outcomes of a Randomized Phase III Trial Comparing Adjuvant Chemotherapy With S-1 Versus Surgery Alone in Stage II or III Gastric Cancer

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See accompanying editorial on page 4348; listen to the podcast by Dr Mayer at www.jco.org/podcast

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ABSTRACT

Purpose
The first planned interim analysis (median follow-up, 3 years) of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer confirmed that the oral fluoropyrimidine derivative S-1 significantly improved overall survival, the primary end point. The results were therefore opened at the recommendation of an independent data and safety monitoring committee. We report 5-year follow-up data on patients enrolled onto the ACTS-GC study.

Patients and Methods
Patients with histologically confirmed stage II or III gastric cancer who underwent gastrectomy with D2 lymphadenectomy were randomly assigned to receive S-1 after surgery or surgery only. S-1 (80 to 120 mg per day) was given for 4 weeks, followed by 2 weeks of rest. This 6-week cycle was repeated for 1 year. The primary end point was overall survival, and the secondary end points were relapse-free survival and safety.

Results
The overall survival rate at 5 years was 71.7% in the S-1 group and 61.1% in the surgery-only group (hazard ratio [HR], 0.669; 95% CI, 0.540 to 0.828). The relapse-free survival rate at 5 years was 65.4% in the S-1 group and 53.1% in the surgery-only group (HR, 0.653; 95% CI, 0.537 to 0.793). Subgroup analyses according to principal demographic factors such as sex, age, disease stage, and histologic type showed no interaction between treatment and any characteristic.

Conclusion
On the basis of 5-year follow-up data, postoperative adjuvant therapy with S-1 was confirmed to improve overall survival and relapse-free survival in patients with stage II or III gastric cancer who had undergone D2 gastrectomy.

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INTRODUCTION

In 2008, there were 737,000 deaths from gastric cancer worldwide. Gastric cancer is the second leading cause of cancer-related death, with the highest mortality rates in East Asia, including Japan, Korea, and China (28.1 per 100,000 in males; 13.0 per 100,000 in females).[1] Approximately 60% of gastric cancers in the world are diagnosed in this area. The mainstay of treatment for gastric cancer is surgery. However, in stages II (excluding T1 disease) and III (moderately advanced), an appreciable proportion of patients have recurrence, even after curative resection. Consequently, various regimens for adjuvant chemotherapy have been implemented to prevent postoperative recurrence.

Although the results of many randomized, controlled studies conducted to verify the effectiveness of postoperative adjuvant chemotherapy for gastric cancer were negative on an individual study basis, meta-analyses of these results have suggested that postoperative adjuvant chemotherapy is therapeutically useful in patients with gastric cancer.[2-7] However, no regimens have been clearly recommended for adjuvant chemotherapy after gastrectomy with D2 lymphadenectomy (D2 gastrectomy), established as the standard procedure for advanced gastric cancer in East Asia.

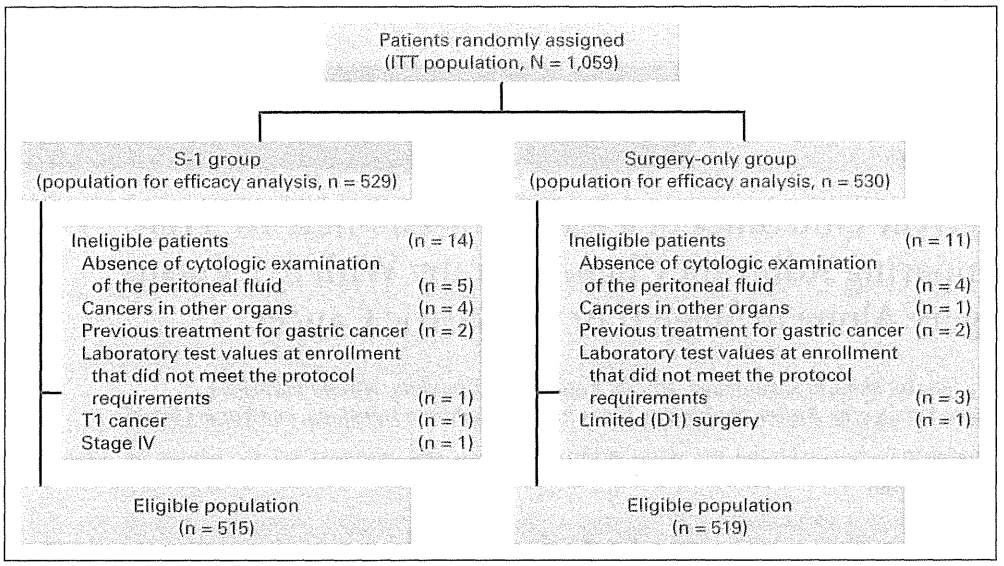

Fig 1. CONSORT diagram. D1 gastrectomy; ITT, intent-to-treat.

The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) is a randomized phase III trial to confirm the effectiveness of 1-year postoperative treatment with S-1 compared with surgery alone in patients with stage II or III gastric cancer who underwent D2 gastrectomy. S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) is a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine preparation combining tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1.[8,9] Two phase II studies[10,11] in patients with advanced or recurrent gastric cancer obtained high response rates exceeding 40%. Postoperative adjuvant chemotherapy with S-1 was thus expected to be effective.

In this phase III trial, 1,059 patients with histologically confirmed stage II or III gastric cancer who underwent D2 gastrectomy were enrolled. A protocol-based interim analysis performed 1 year after the completion of enrollment (median follow-up, 3 years) confirmed that S-1 was effective. Because statistical analysis indicated that there was minimal probability that the results of this study would turn out to be negative after 5 years of follow-up, an independent data and safety monitoring committee recommended that the results should be disclosed at that time. An analysis of the results available at that time showed that the 3-year overall survival (OS) was 80.1% in the S-1 group compared with 70.1% in the surgery-only group. S-1 was demonstrated to reduce the risk of death by 32% (hazard ratio [HR], 0.68; 95% CI, 0.52 to 0.87; $P = .003$).[12] Although the study results were disclosed early because of these promising results, we considered it important to have 5-year follow-up data available. Such data would facilitate a comparison of our results for 5-year OS and other outcomes with those of previous trials. Moreover, this analysis may justify

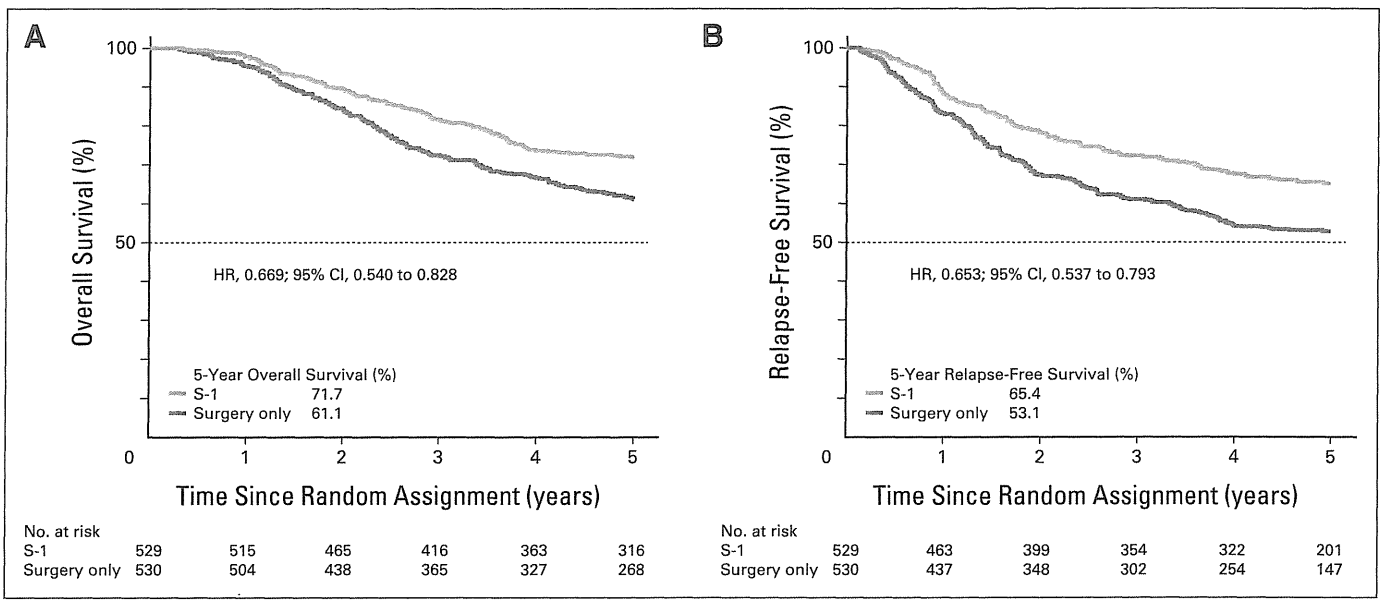

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for all randomly assigned patients. HR, hazard ratio.

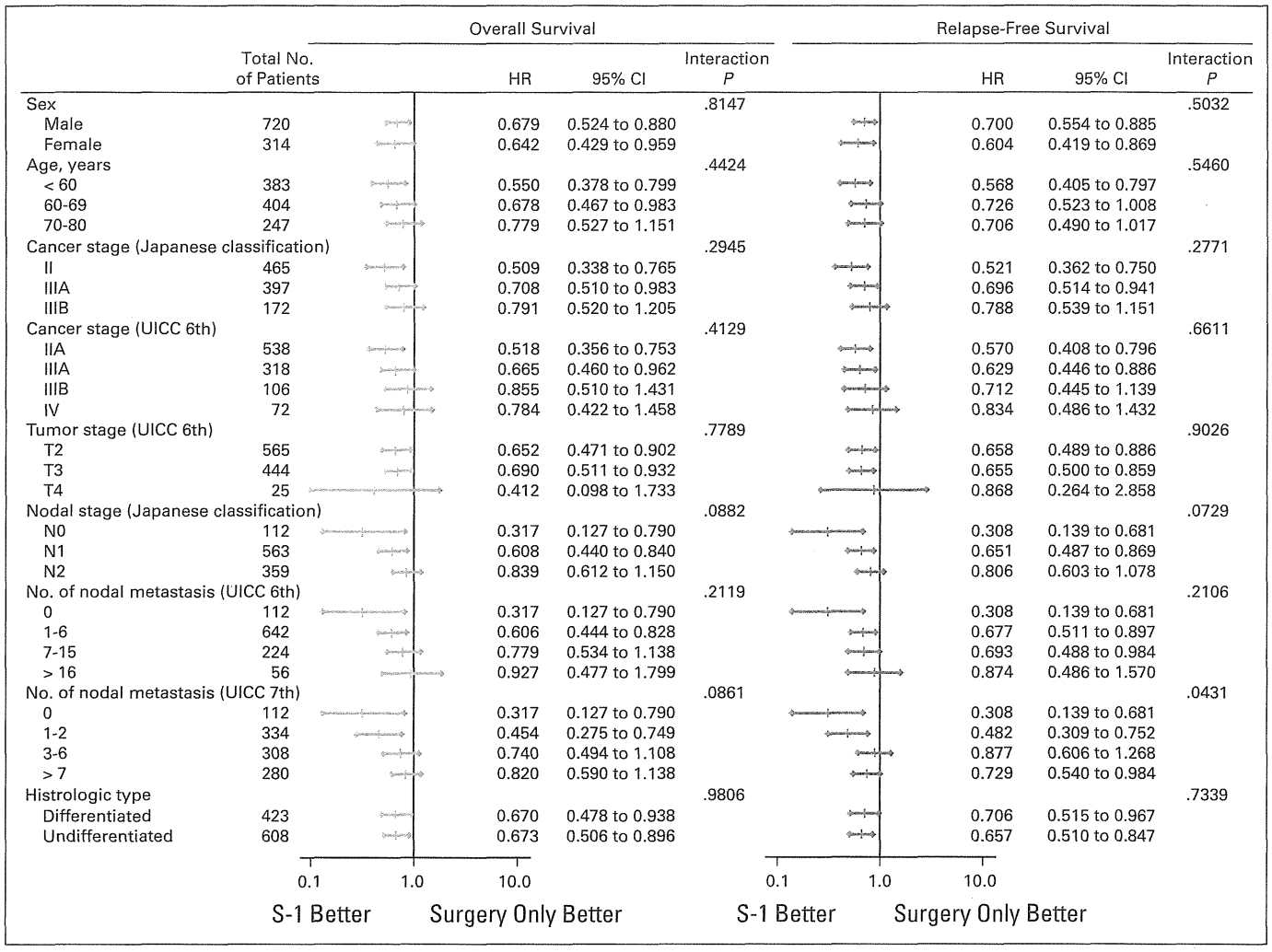

Fig 3. Subgroup analysis: overall survival and relapse-free survival for eligible population. In the surgery-only group, cancers in three patients could not be classified as differentiated or undifferentiated. HR, hazard ratio; UICC, International Union Against Cancer (UICC) TNM Classification of Malignant Tumours.

the present controversial use of 3-year relapse-free survival (RFS) as the primary end point in clinical trials of adjuvant chemotherapy for potentially curable gastric cancer.

PATIENTS AND METHODS

The trial was conducted in accordance with the World Medical Association Declaration of Helsinki and Japanese Good Clinical Practice guidelines. This protocol was approved by the institutional review board of each participating hospital (see Data Supplement). Written informed consent was obtained from all patients. Tumor stage classification and D classification were in accordance with the Japanese Classification of Gastric Carcinoma (Second English Edition).[13]

Patients and Treatment

Eligibility criteria were as follows: a histopathologically confirmed diagnosis of stage II (except for T1 disease), IIIA, or IIIB gastric cancer; R0 resection (with no tumor cells at the margin) with D2 or more extensive lymph node dissection; no evidence of hepatic, peritoneal, or distant metastasis; no tumor cells in peritoneal fluid on cytologic analysis; age 20 to 80 years; no previous treatment for cancer except for the initial gastric resection for the primary lesion; and adequate organ function. Patients were enrolled within 6 weeks after surgery over the telephone or by means of facsimile. Patients were randomly assigned to either the S-1 group or the surgery-only group. The assignments were made by the minimization method according to disease stage (II, IIIA, or IIIB) at the ACTS-GC data center.

Patients assigned to the S-1 group received S-1 in a daily dose of 80, 100, or 120 mg in two divided doses. The dose of S-1 was assigned on the basis of body surface area. S-1 was given for 4 weeks, followed by 2 weeks of rest. Treatment was continued for 1 year after surgery. Patients assigned to the surgery-only group received no anticancer treatment postoperatively until the confirmation of recurrence. The criteria for dose reduction and toxicity were described previously.[12]

Follow-Up

In the S-1 group, the results of blood tests and clinical findings were assessed at 2-week intervals during treatment with S-1. In the surgery-only group, patients came to the hospital for re-examination at least once every 3 months for the first year after surgery. From the second year onward, all patients were followed up in the same manner. Relapse was confirmed by imaging studies, including ultrasonography, computed tomography, and GI radiography, as well as endoscopy. Patients underwent at least one imaging study at 6-month intervals for the first 2 years after surgery and at 1-year intervals until 5 years after surgery. Individual patients were followed up for 5 years from the date of random assignment.

Statistical Analysis

The sample size was calculated as follows. Given that the 5-year survival rate would be 70% in the surgery-only group, with an HR of 0.70, $\alpha = .05$ (two-sided), and a statistical power of 80%, we estimated that 1,000 patients would be required. OS and RFS were estimated on the basis of all randomly assigned patients. The results in eligible patients were analyzed according to disease stage. OS was defined as the interval from the date of random assignment to the date of death from any cause. RFS was defined as the interval from the date of random assignment to the date of confirming recurrence or death from any cause, whichever came first. Data for up to 5 years from the date of random assignment were analyzed. Data obtained after 5 years were not included in this analysis. The survival rate was estimated by using the Kaplan-Meier method. The Cox proportional hazards model was used to calculate HRs. All statistical analyses were done with SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients

From October 2001 through December 2004, a total of 1,059 patients were enrolled at 109 centers throughout Japan; 529 were assigned to the S-1 group and 530 to the surgery-only group (intention-to-treat population; Fig 1). In both groups combined, 474 patients (44.8%) had stage II disease, 409 (38.6%) had stage IIIA disease, and 175 (16.5%) had stage IIIB disease. The numbers of patients with each stage of disease were similar in the two treatment groups. The groups were also well balanced with respect to the type of gastrectomy performed, the combined resection of other organs, and other factors. Details of the patient demographics and baseline characteristics have been reported previously.[12]

Fourteen patients in the S-1 group and 11 in the surgery-only group were ineligible, as shown in Figure 1. In the S-1 group, 12 patients did not receive S-1. In the surgery-only group, four patients received adjuvant treatment at their strong request, violating the protocol.

Safety

Details of the safety analysis have been reported previously.[12] In brief, except for anorexia (incidence, 6%), grade 3 or 4 adverse events occurred in less than 5% of the patients in the S-1 group.

OS and RFS in All Randomly Assigned Patients

Among 1,059 patients, 145 and 199 died, 32 and 42 patients are alive with recurrence, and 352 and 289 patients are alive without recurrence in the S-1 and the surgery-only groups, respectively. Data on 131 patients lost to follow-up within 5 years from the date of random assignment were censored.

OS and RFS were analyzed in all 1,059 randomly assigned patients. The 5-year OS rate was 71.7% (95% CI, 67.8% to 75.7%) in the S-1 group and 61.1% (95% CI, 56.8% to 65.3%) in the surgery-only group. The HR for death in the S-1 group compared with the surgery-only group was 0.669 (95% CI, 0.540 to 0.828), indicating that S-1 reduced the risk of death by 33.1% (Fig 2A). The 5-year RFS rate was 65.4% (95% CI, 61.2% to 69.5%) in the S-1 group and 53.1% (95% CI, 48.7% to 57.4%) in the surgery-only group. The HR for relapse in the S-1 group compared with that in the surgery-only group was 0.653 (95% CI, 0.537 to 0.793). Treatment with S-1 thus reduced the risk of relapse by 34.7% (Fig 2B).

Subgroup Analysis

OS and RFS in eligible patients were analyzed according to sex, age, disease stage (Japanese Classification, 13th edition), and histologic type. There was no interaction between treatment and any of these factors (Fig 3). Kaplan-Meier estimates of OS and RFS are shown according to disease stage, which was used as a stratification factor when patients were randomly assigned (Figs 4, 5, and 6).

The 5-year OS rates of the patients with stage II disease were 84.2% (95% CI, 79.5% to 89.0%) in the S-1group and 71.3% (95% CI, 65.3% to 77.2%) in the surgery-only group, with an HR of 0.509 (95% CI, 0.338 to 0.765; Fig 4A). Their 5-year RFS rates were 79.2% (95% CI, 73.8% to 84.6%) in the S-1 group and 64.4% (95% CI, 58.1% to 70.7%) in the surgery-only group, with an HR of 0.521 (95% CI, 0.362 to 0.750; Fig 4B). The 5-year OS rates of stage IIIA patients were 67.1% (95% CI, 60.4% to 73.8%) in the S-1 group and 57.3% (95% CI, 50.3% to 64.2%) in the surgery-alone group, with an HR of 0.708 (95% CI, 0.510 to 0.983; Fig 5A). Their 5-year RFS rates were 61.4% (95% CI, 54.5% to 68.4%) in the S-1 group and 50.0% (95% CI, 42.9% to 57.0%) in the surgery-alone group, with an HR of 0.696 (95% CI,

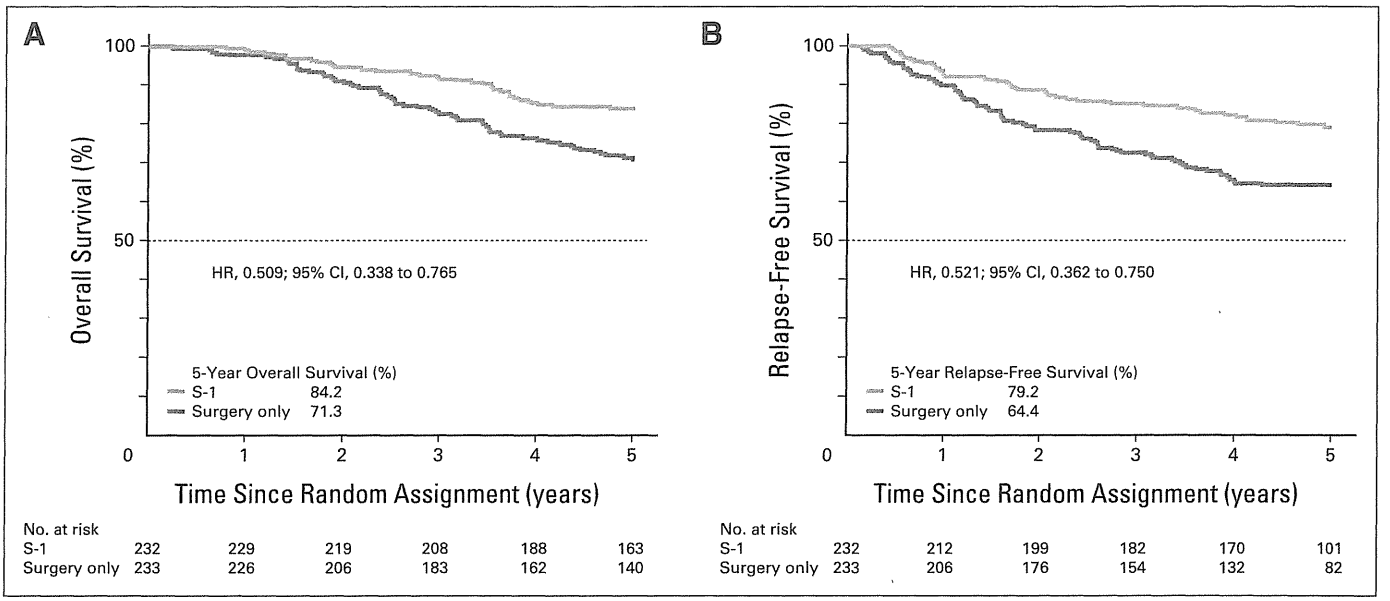

Fig 4. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage II gastric cancer. HR, hazard ratio.

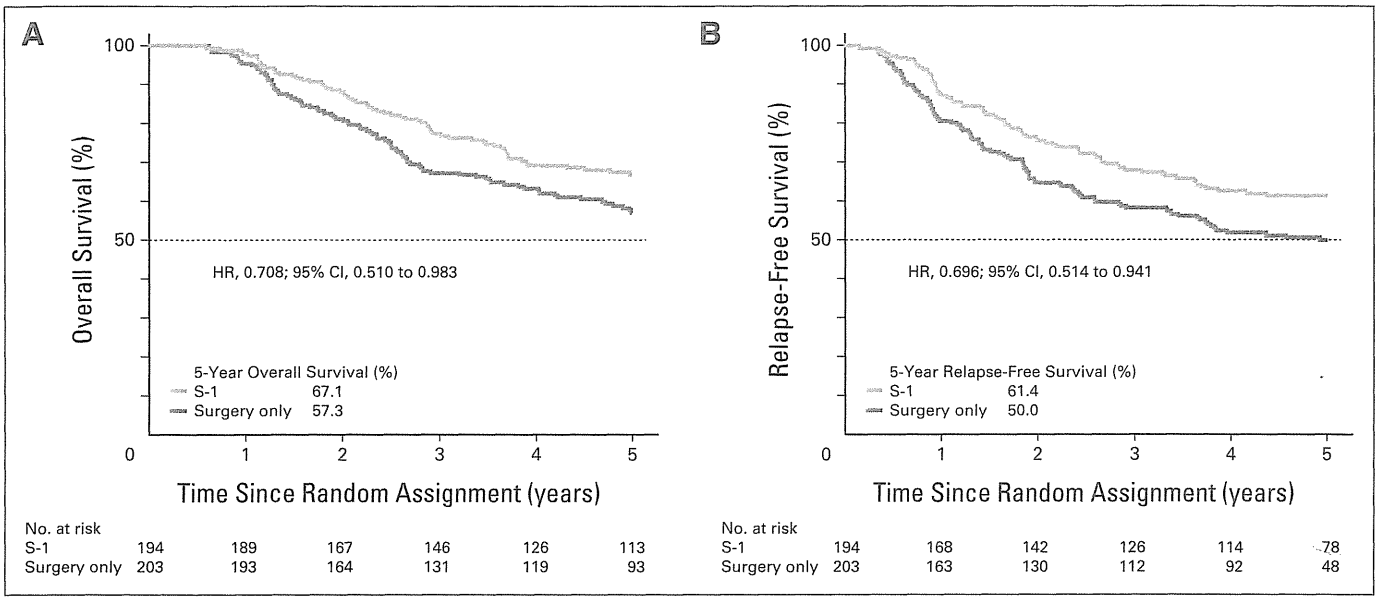

Fig 5. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage IIIA gastric cancer. HR, hazard ratio.

0.514 to 0.941; Fig 5B). As for stage IIIB disease, we enrolled 90 patients in the S-1 group and 85 in the surgery-only group; the 5-year OS rates were 50.2% (95% CI, 39.5% to 61.0%) in the S-1 group and 44.1% (95% CI, 33.1% to 55.0%) in the surgery-alone group, with an HR of 0.791 (95% CI, 0.520 to 1.205; Fig. 6A). Their 5-year RFS rates were 37.6% (95% CI, 27.0% to 48.2%) in the S-1 group and 34.4% (95% CI, 24.1% to 44.7%) in the surgery-alone group, with an HR of 0.788 (95% CI, 0.539 to 1.151; Fig 6B).

Site of First Relapse

Common sites of first relapse were the peritoneum, hematogenous sites, and lymph nodes (Table 1). Rates of metastasis and relapse were consistently lower in the S-1 group than in the surgery-only group for all sites. In particular, the rates of recurrence in lymph nodes and of peritoneal relapse were markedly lower in the S-1 group.

DISCUSSION

To the best of our knowledge, the ACTS-GC study is the first large clinical trial of adjuvant chemotherapy enrolling more than 1,000 patients who underwent D2 gastrectomy for gastric cancer. The results of this follow-up study showed that 1-year treatment with S-1 improved OS and RFS at 5 years compared with surgery alone, thus reconfirming the conclusions reached on early publication of the study results after a median follow-up of 3 years.

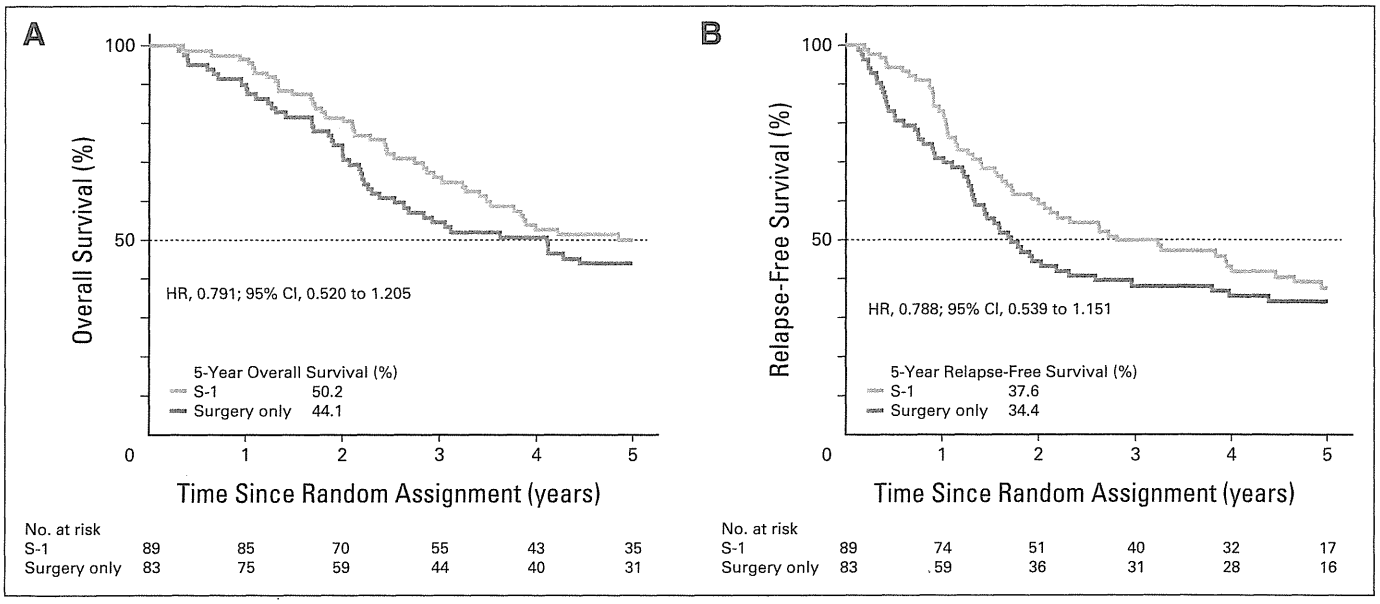

Fig 6. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage IIIB gastric cancer. HR, hazard ratio.

Table 1. Site of First Relapse (all randomly assigned patients)*

Site	S-1 (n = 529) No.	S-1 (n = 529) %	Surgery Only (n = 530) No.	Surgery Only (n = 530) %	HR	95%CI
Total No. of relapses	162	30.6	221	41.7	—	—
Local	11	2.1	17	3.2	0.572	0.268 to 1.221
Lymph nodes	30	5.7	54	10.2	0.505	0.323 to 0.789
Peritoneum	77	14.6	100	18.9	0.687	0.511 to 0.925
Hematogenous	61	11.5	71	13.4	0.784	0.557 to 1.105

Abbreviation: HR, hazard ratio.
*Some patients had a first relapse at more than one site.

Our present results confirmed that postoperative adjuvant chemotherapy with S-1 alone reduced the risk of death by 33.1%, thereby demonstrating that effectiveness was maintained since the previous analysis. This reduction in the risk of mortality is comparable with that obtained with combined regimens for adjuvant chemotherapy in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[14] and the Intergroup 0116 (INT-0116) trial.[15]

Whether the results of this study can be extrapolated to countries outside East Asia remains uncertain because of possible differences in pharmacokinetics of S-1 between whites and East Asians. If S-1 is used as adjuvant chemotherapy in whites, the dose should be carefully adjusted. A second reason is that all patients in this study underwent D2 gastrectomy although more limited surgery (D0/1) is commonly performed in the United States and some parts of Europe. In the surgery-only group, OS at 5 years was 61.1%, which was much better than that of patients undergoing D2 gastrectomy in Europe (33%) in a Dutch trial.[16] One of the reasons for this large difference may be the high level and widespread use of diagnostic technology in Japan, potentially leading to stage migration between Japan and Western countries.[17] Another important reason might be the high quality of D2 gastrectomy in Japan, whereas D0 or D1 gastrectomy remains the standard procedure in the United States and was the standard in Europe until recently. Although a Dutch trial comparing D1 with D2 gastrectomy reported negative results,[16,18] a 15-year follow-up study showed that the rate of mortality from gastric cancer was significantly lower in the D2 gastrectomy group.[19] Thus, the most recent European Society for Medical Oncology (ESMO) clinical practice guidelines recommend D2 gastrectomy as the standard procedure for curable advanced gastric cancer.[20]

The primary end point of this study was 5-year OS, although that of an ongoing adjuvant chemotherapy study in Korea and China is 3-year disease-free survival. The latter is designed to evaluate the efficacy of postoperative adjuvant chemotherapy with capecitabine and oxaliplatin compared with surgery alone. To justify the use of RFS or disease-free survival as the primary end point for adjuvant chemotherapy after curative resection of gastric cancer, more evidence is needed, but the results of this study may strongly suggest that RFS can be used as the primary end point of such studies. (In this follow-up analysis, the 3-year RFS rates were 72.4% and 61.1%, and the 5-year OS rates were 71.7% and 61.1% in the S-1 group and surgery-only group, respectively.)

To compare our results with those of other foreign studies, we also report the stage-specific 3- and 5-year OS and RFS according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours, Sixth Edition. Three-year OS rates according to UICC staging in the S-1 and surgery-only groups were 91.1% and 80.9% (stage II), 77.8% and 68.3% (stage IIIA), 66.6% and 56.8% (stage IIIB), and 59.1% and 45.7% (stage IV). Three-year RFS rates were 84.3% and 73.5% (stage II), 69.1% and 56.7% (stage IIIA), 44.8% and 28.9% (stage IIIB), and 46.0% and 37.1% (stage IV). Five-year OS rates were 83.4% and 70.8% (stage II), 68.9% and 56.2% (stage IIIA), 43.7% and 40.1% (stage IIIB), and 45.1% and 42.7% (stage IV). Five-year RFS rates were 77.9% and 65.4% (stage II), 64.3% and 48.7% (stage IIIA), 35.9% and 28.9% (stage IIIB), and 26.8% and 25.0% (stage IV).

The approach for adjuvant chemotherapy differs among East Asian countries, including Japan, in which D2 gastrectomy has long been the standard procedure, and Western countries, in which D0 or D1 gastrectomy used to be or currently is standard. As Cunningham and Chua[21] stated, "surgery alone" is no longer standard treatment anywhere in the world for advanced gastric cancer. Some type of adjuvant chemotherapy, including the use of radiotherapy after D0/1 resection, can thus be considered standard treatment at present.

A meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group[7] showed that some form of postoperative chemotherapy is associated with a higher survival rate than surgery alone; moreover, the use of monotherapy for postoperative adjuvant treatment resulted in good outcomes. The ACTS-GC trial demonstrated that S-1 monotherapy improved OS and RFS. In patients with early-stage (II and IIIA) tumors, the benefits of treatment with S-1 were considerable. However, the 5-year OS rate in patients with stage IIIB disease was 50.2% in the S-1 group and 44.1% in the surgery-only group, suggesting that there remains some room for improvement. Future studies should evaluate the effectiveness of intensive preoperative and/or postoperative chemotherapy with multiple agents in patients at high risk for relapse.

The results of the S-1 plus cisplatin versus S-1 in randomized controlled trial in the treatment for stomach cancer (SPIRITS) trial,[22] demonstrating that S-1 plus cisplatin is superior to S-1 alone with respect to survival in patients with unresectable or recurrent gastric cancer, and the V325 study [a randomized, multinational phase II/III trial of patients with untreated advanced gastric cancer],[23,24] showing that the addition of docetaxel to cisplatin plus fluorouracil prolongs survival, indicated that S-1 plus cisplatin and S-1 plus docetaxel are candidate regimens for postoperative adjuvant chemotherapy. These regimens were confirmed to be feasible in a postoperative setting,[25,26] and further studies should be performed to examine whether such regimens are superior to S-1 alone.

The Japan Clinical Oncology Group (JCOG) is now performing the JCOG 0501 study to compare S-1 plus cisplatin as neoadjuvant chemotherapy with surgery followed by S-1 monotherapy in patients with clinically resectable Borrmann type 4 (linitis plastica) and large type 3 gastric cancer. This trial is expected to be a landmark study, determining the future direction for preoperative chemotherapy in Japan.

The use of molecular targeted agents for gastric cancer has been studied extensively. In the Trastuzumab in Combination with Chemotherapy Versus Chemotherapy Alone for Treatment of HER2-Positive Advanced Gastric or Gastro-Esophageal Junction Cancer (ToGA) study, trastuzumab combined with cisplatin and either fluorouracil or capecitabine significantly prolonged OS in patients with HER2-positive gastric cancer.[27] The effectiveness of adjuvant chemotherapy with molecular targeted agents such as trastuzumab also needs to be assessed in patients with HER2-positive gastric cancer.

In conclusion, this 5-year follow-up study confirmed that adjuvant chemotherapy with S-1 given for 1 year after surgery improved

