Table 3 Response rate

	Four-weekly regimen cohort 1		Biweekly regimen cohort 2	
	No. of patients	%	No. of patients	%
Total	27		25	
CR	0	0	0	0
PR	7	26	7	28
SD	10	37	9	36
PD	10	37	9	36
RR		26		28
DCR		63		64

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *RR* response rate, *DCR* disease control rate

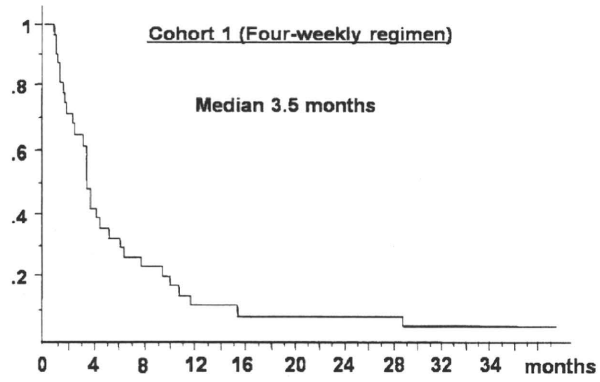

Fig. 1 Kaplan–Meier curve for progression-free survival curve in cohort 1. Median progression-free survival was 3.5 months

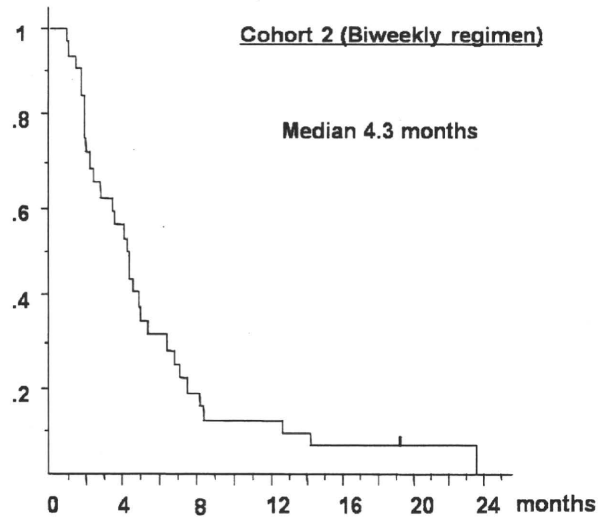

Fig. 2 Kaplan–Meier curve for progression-free survival curve in cohort 2. Median progression-free survival was 4.3 months

Fig. 3 Kaplan–Meier curve for overall survival curve in cohort 1. Median overall survival was 9.5 months

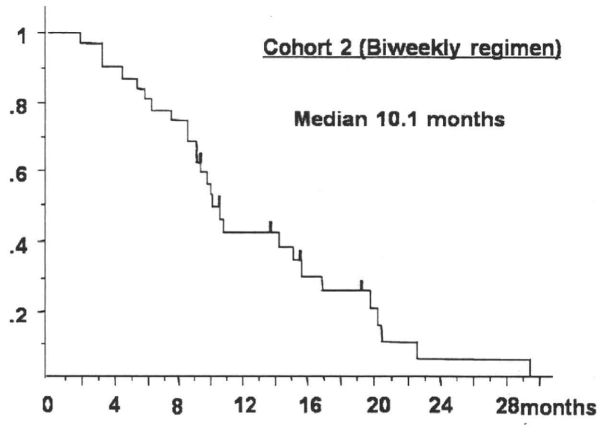

Fig. 4 Kaplan–Meier curve for overall survival curve in cohort 2. Median overall survival was 10.1 months

81% and 53% for neutropenia 45% and 28% for anemia, respectively. Incidences of grade 3 nausea were 23% and 12%, of grade 3 vomiting 23% and 9%, and of grade 3 anorexia 19% and 12%, respectively. No grade 4 nonhematological toxicities or treatment-related deaths occurred in this series.

Dose intensity

In cohort 1, the total number of courses was 67. Dose reduction of CPT-11 was required in 7 (23%) patients. The total number of skipped CPT-11 scheduled on day 15 was 10. Leukopenia was the most frequent reason for skipping the dose and for dose reduction. Thus, the actual dose intensity of CPT-11 was 24.5 mg/m^2 per week, whereas that of CDDP was 15.4 mg/m^2 per week. These values correspond to 70% and 77% of the planned doses, respectively.

In cohort 2, the total number of courses was 283. Dose reduction of CPT-11 was required in 5 (16%) patients. The total number of delays in treatment schedule was 24 (8%). Leukopenia was the most frequent reason both for

Table 4 Adverse events

	Four-weekly regimen (cohort 1)					Biweekly regimen (cohort 2)				
	Grade 3		Grade 4		Grade 3–4	Grade 3		Grade 4		Grade 3–4
	No.	%	No.	%	%	No.	%	No.	%	%
Hematological										
Leukopenia	16	52	7	22	74	12	38	2	6	44
Neutropenia	3	10	22	71	81	13	41	4	12	53
Anemia	9	29	5	16	45	6	19	3	9	28
Thrombocytopenia	2	6	0	0	6	2	6	1	3	9
Nonhematological										
Nausea	7	23	0	0	23	4	12	0	0	12
Vomiting	7	23	0	0	23	3	9	0	0	9
Anorexia	4	13	2	6	19	4	12	0	0	12
Diarrhea	1	3	0	0	3	0	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	0	0
Febrile neutropenia	2	6	0	0	0	2	6	0	0	6

Table 5 Subsequent chemotherapy

	Four-weekly regimen (cohort 1) ($n = 31$)		Biweekly regimen (cohort 2) ($n = 32$)	
	No. of patients	%	No. of patients	%
No. of regimens				
0 (BSC)	8	26	7	22
1	8	26	20	63
2	10	32	4	13
3	4	13	1	3
No follow-up	1	3	0	0
Regimen				
Paclitaxel	21	68	18	58
Contained 5-FU bolus	7	23	7	
mFOLFOX6	0	0	2	6
5-FU i.a. (WHF)	0	0	2	6
Oral fluoropyrimidine	0	0	2	6
CDDP i.p.	4	13	0	0
MMC	3	10	0	0
Others	2	6	1	3

i.a. intra-arterial injection, *mFOLFOX6* 5-fluorouracil (5-FU), leucovorin, and oxaliplatin, *WHF* weekly high dose 5-FU, *i.p.* intraperitoneal injection, *MMC* mitomycin C

treatment delay and dose reduction. Thus, the dose intensity of CPT-11 was 27.1 mg/m^2 per week, whereas that of CDDP was 14.1 mg/m^2 per week. These values correspond to 90% and 94% of the planned doses, respectively.

Subsequent chemotherapy

Subsequent chemotherapies administered in each cohort are summarized in Table 5. Twenty-three patients (74%) in cohort 1 and 25 (81%) in cohort 2 received subsequent chemotherapy. Eighteen patients (58%) in cohort 1 and 21 (68%) in cohort 2 received monotherapy with paclitaxel.

Discussion

There are few reports of CPT-11 alone for pretreated patients with advanced gastric cancer. Futatsuki et al. [13]

reported a response rate of 20% as a CPT-11 single agent in pretreated patients. For combination therapy with CPT-11 and CDDP, administration by 4-weekly or biweekly regimen has been widely used after the failure of S-1 or 5-FU monotherapy. Boku et al. [9] reported a response rate of 27% in a prospective study examining administration by 4-weekly regimen, and Ueda et al. [10] recapitulated these results with a response rate of 28% in a retrospective analysis of their clinical practice. On the other hand, response rates of 20–29% have been reported for administration of a biweekly regimen [11, 14, 15]. Although a randomized trial in pretreated patients with advanced gastric cancer has not yet been performed, combination therapy with CPT-11 plus CDDP seems to be more effective than CPT-11 alone, at least with regard to the response rate. CPT-11 plus CDDP seems to be one of the most common chemotherapy regimens after failure in first-line chemotherapy of S-1 or 5-FU alone.

In our clinical practice, in 2007, we replaced the administration of CPT-11 plus CDDP on a 4-weekly regimen with a biweekly regimen. Consequently, the clinical outcomes of the administration of these agents every 4 weeks or every 2 weeks were not simultaneously compared. Because the administration of CPT-11 is contraindicated for patients with complications myelosuppression, infection, diarrhea, ileus, interstitial pneumonia, or obstructive jaundice due to its severe toxicity, we limited the administration of CPT-11 for both second- and third-line chemotherapy to patients with a PS 0–2 and no or only mild peritoneal dissemination in clinical practice. There seemed to be no intended differences in indication between these two cohorts. However, cohort 2 included more patients in a third-line setting and with PS 2 than did cohort 1. Actually, the patient background was rather worse in cohort 2 than in cohort 1.

Despite these background differences, RR, PFS, and OS of cohort 2 were comparable with those of cohort 1. These parameters seem to be consistent with those in previous reports of CPT-11 plus CDDP administered on a biweekly regimen. In this study, the incidence of grade 3 or 4 toxicities was lower in cohort 2 than in cohort 1. In particular, the incidences of grade 4 leukopenia (74% vs. 44% for cohort 1 and 2, respectively), neutropenia (81% vs. 53%), grade 3 nausea (23% vs. 12%), and grade 3 vomiting (23% vs. 9%) were much higher in cohort 1. These toxicities sometimes caused dose reduction and skipped administrations. Dose intensities of CPT-11 and CDDP in cohort 2 were equivalent to those in cohort 1, although the planned doses were higher in cohort 1 than in cohort 2. These results suggest that a biweekly regimen might exert a comparable activity to a 4-weekly regimen, in addition to being more feasible.

For second-line chemotherapy after the failure of fluoropyrimidine-based chemotherapy, taxanes (paclitaxel and docetaxel) are another option. Arai et al. [16] reported that the RR of paclitaxel in heavily treated patients was 23% and the median survival was 6.9 months. These results seem comparable with those for CPT-11-containing chemotherapy as a second-line treatment for advanced gastric cancer. Whereas a randomized phase III trial of CPT-11 versus paclitaxel in a second-line setting after failure of first-line chemotherapy with fluoropyrimidine and platinum is ongoing in Japan [West Japan Oncology Group (WJOG) 4007]. Today in Japan, combination therapy with S-1 and CDDP is recognized as the standard first-line therapy for advanced gastric cancer. In this situation, CPT-11 plus CDDP is not applicable in a second-line setting for many initially unresectable patients. However, for patients who develop recurrence during or immediately after adjuvant therapy with S-1, combination therapy with CPT-11 and CDDP might be a promising regimen. Another phase III trial comparing taxane and CPT-11 plus CDDP is also underway for patients in whom S-1 monotherapy has failed, especially in an adjuvant setting.

In conclusion, this study suggests that administration of CPT-11 plus CDDP on a biweekly regimen might have comparable activity with administration of these agents on a 4-weekly regimen, in addition to being associated with milder toxicities. A biweekly regimen could be considered as the preferred test arm in a comparison with a 4-weekly regimen in future trials.

Conflict of interest statement No author has any conflict of interest.

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Original Article

Phase I Study of Docetaxel, Cisplatin and S-1 in Patients with Advanced Gastric Cancer

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Objective: S-1 plus cisplatin is standard treatment for advanced gastric cancer in Japan. Triplet therapy with docetaxel, cisplatin and fluoropyrimidine showed a survival benefit over doublet therapy, but was associated with substantial toxicities. We investigated the maximum tolerated dose of combination chemotherapy with divided-dose docetaxel added to standard-dose S-1 plus cisplatin in advanced gastric cancer patients.

Methods: Patients with advanced gastric cancer, naive to chemotherapy or not refractory to fluoropyrimidine, were enrolled. Fixed doses of S-1 (40 mg/m^2 twice daily for 3 weeks) and cisplatin (60 mg/m^2 on day 1) were administered with increasing docetaxel dose levels of 20 mg/m^2 (dose level 1), 25 mg/m^2 (dose level 2) and 30 mg/m^2 (dose level 3) on days 1, 8 and 15, or 40 mg/m^2 (dose level 4) on days 1 and 15 of a 5-week cycle. Treatment cycles were repeated until disease progression, patient's refusal or unacceptable toxicity occurred.

Results: Fifteen patients were enrolled. During the first cycle, no dose-limiting toxicity was observed at dose levels 1 and 2. At dose level 3, grade 3 febrile neutropenia was seen in one patient. At dose level 4, grade 3 infection and grade 3 abdominal pain were observed. Thus, dose level 4 was determined to be the maximum tolerated dose. The response rate was 54% (7/13), and median progression-free survival and overall survival were 243 and 383 days, respectively.

Conclusions: The recommended dose of docetaxel added to standard-dose S-1 (80 mg/m^2 days 1–21) plus cisplatin (60 mg/m^2 day 1) was 40 mg/m^2 on days 1 and 15 of a 5-week cycle.

Key words: docetaxel – cisplatin – s-1 – DCS – gastric cancer

INTRODUCTION

Gastric cancer is more prevalent in Eastern Asia, Eastern Europe and Central and South America than in other regions. In Japan, gastric cancer is the second most frequent cause of cancer mortality, accounting for 50 597 of the 336 468 cancers occurring in 2007 (1). Because of the vague and non-specific symptoms associated with gastric cancer, the disease is often advanced at the time of diagnosis. Despite the identification and development of several new types of anti-cancer agents, gastric cancer remains an aggressive malignancy with a median survival of 9–13 months in patients with metastatic or recurrent disease (2–5).

There is no global consensus on a standard regimen for gastric cancer; however, a combination of 5-fluorouracil (5-FU) plus cisplatin is the most commonly used treatment worldwide. In Japan, 5-FU alone was used as the control

arm in clinical trials based on the results of the JCOG9205 trial (6). The subsequent trial, JCOG9912, was started in 1999 and compared 5-FU alone with CPT-11 plus cisplatin or S-1 alone. The results showed that S-1 was not inferior to 5-FU alone, although CPT-11 plus cisplatin did not show superiority (4). Subsequently, the SPIRITS trial comparing S-1 alone with S-1 plus cisplatin showed the superiority of S-1 plus cisplatin to S-1 alone (5). From the results of these randomized trials, S-1 plus cisplatin was recognized as the new standard of care for advanced gastric cancer in Japan.

Docetaxel monotherapy used to treat advanced gastric cancer yielded response rates of 17–24% in phase II trials (7–9). Recently, several results of randomized trials with docetaxel in combination with fluorouracil plus cisplatin were reported. The V325 study demonstrated the superiority of docetaxel (75 mg/m^2, thrice weekly) in combination with 5-FU plus cisplatin (DCF) to 5-FU plus cisplatin (CF) in the time to progression, overall survival and response rate (2). However, the toxicity of DCF caused a higher incidence of severe neutropenia than CF, and the authors emphasized the need for vigilant patient selection and education, monitoring and active management. Roth et al. (10) reported on a randomized phase II study comparing three chemotherapy regimens; TCF (docetaxel, 85 mg/m^2 at initiation then a dose reduction to 75 mg/m^2, thrice weekly, with cisplatin and fluorouracil), TC (docetaxel and cisplatin) and ECF (epirubicin, cisplatin and fluorouracil). Although the efficacy of TCF was more promising than that of TC, docetaxel-containing regimens were associated with more severe haematological toxicity than ECF. From the results of these two studies, it was thought that adding thrice-weekly docetaxel (75 mg/m^2) to cisplatin and 5-FU is highly effective in advanced gastric cancer, although it is associated with a high incidence of haematological toxicity. However, the triplet regimen including thrice-weekly docetaxel has not been generally accepted as a new standard of treatment because of its substantial toxicity.

For advanced non-small cell lung cancer, several randomized phase II or III trials of weekly docetaxel compared with thrice-weekly docetaxel in the second-line setting were reported (11–16). A meta-analysis of these randomized studies demonstrated that grade 3 neutropenia was significantly less with weekly docetaxel than with thrice-weekly docetaxel, while overall survival did not significantly differ between the two schedules (relative risk was 1.01) (17).

From these results, it is speculated that divided doses of docetaxel can reduce the toxicity while preserving its activity. In order to reduce the severe haematological toxicity of a triplet regimen, we conducted a phase I study of divided-dose docetaxel in combination with the standard treatment schedule of S-1 plus cisplatin for advanced gastric cancer. The primary endpoint was to determine the maximum tolerated dose (MTD) of this regimen in patients with advanced gastric cancer. Secondary endpoints were toxicity and the response rate.

PATIENTS AND METHODS

Patient Eligibility

This study was conducted at Shizuoka Cancer Center, Shizuoka, Japan, and Aichi Cancer Center, Aichi, Japan. To be eligible, patients had to meet the following eligibility criteria: (i) have histologically proven metastatic or recurrent gastric cancer, (ii) be between the ages of 20–75 years, (iii) have a performance status of 1 or less according to the Eastern Clinical Oncology Group (ECOG) scale, (iv) an estimated life expectancy of >8 weeks, (v) no prior chemotherapy or no evidence of resistance to fluoropyrimidines (more than 6 months after the last administration if a patient had received monotherapy with fluoropyrimidine in the adjuvant or neo-adjuvant setting), (vi) adequate bone marrow function (a white blood cell count >4000 and <12 000/mm^3, neutrophil count >2000/mm^3, platelet count >100 000/mm^3), (vii) adequate hepatic function [a serum total bilirubin level ≤1.2 mg/dl, asparate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤100IU/l], (viii) adequate renal function (a serum creatinine level of ≤1.2 mg/dl, creatinine clearance by Cockcroft–Gault Equation >60 ml/min), (ix) an assessable lesion [measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.0 (18) was not mandatory] and (x) provide written informed consent.

The exclusion criteria were as follows: (i) patients with an active infection, (ii) severe peritoneal dissemination with subileus or massive ascites, (iii) marked pleural effusion, (iv) metastasis to the central nerve system, (v) mental disorder, (vi) watery diarrhoea, (vii) interstitial pneumonia, (viii) severe comorbidities such as heart disease or renal disease, (ix) active concomitant malignancy or were (x) pregnant or lactating women or women of childbearing age, unless they were practising effective contraception.

Administration and Dose Escalation

S-1 (Taiho Pharmaceutical Company, Tokyo, Japan) was given orally twice daily for the first 3 weeks of a 5-week cycle. The dose of S-1 administered each time was determined according to the patient's body surface area as follows: <1.25 m^2, 40 mg; 1.25–1.50 m^2, 50 mg and >1.5 m^2, 60 mg. Docetaxel (Sanofi-aventis K.K., Tokyo, Japan) was given as a 1-hour intravenous infusion followed by cisplatin (Bristol-Myers Squibb Company, Tokyo, Japan) 60 mg/m^2 given as a 2-hour intravenous infusion on day 1 of each cycle.

Initially, this study was started with three dose levels of weekly docetaxel given on days 1, 8 and 15 every 5 weeks at dose levels of 20 mg/m^2 (DL1), 25 mg/m^2 (DL2) and 30 mg/m^2 (DL3). Three patients were initially enrolled at each DL. If none experienced a DLT during the first cycle, the next cohort of patients was treated at the subsequent DL. If one or two of the three patients at each DL experienced any DLT, an additional three patients were enrolled at the same DL, and

then if less than two of six patients experienced any DLT, the next cohort was started at the next higher DL.

However, the protocol was amended after DLT evaluation to DL2, because two of six patients (one at DL1 and another at DL2) refused treatment due to severe fatigue after the second cycle. We believe the severe fatigue was caused by the weekly schedule of docetaxel (19). Thus, the protocol was amended and DL4 of docetaxel (40 mg/m^2) was administered on days 1 and 15 every 5 weeks with a fixed dose of S-1 plus cisplatin. Actually the dose intensity of docetaxel at DL4 (16 mg/m^2/week) was less than DL3 (18 mg/m^2/week). Simultaneously, in the protocol amendment, if less than two of the initial three patients at DL3 experienced any DLT, the subsequent patients were enrolled at DL4 because of the lower dose intensity at DL4 than at DL3. The recommended dose (RD) for the next trial was defined as the DL at which less than two of six patients experienced DLT. No intra-subject dose escalation was performed.

If patients had counts of leukocytes $<2000/mm^3$, platelets $<50\,000/mm^3$, total bilirubin of >1.5 mg/dl, serum creatinine of >1.5 mg/dl or non-haematological toxicity (nausea, vomiting, diarrhoea, stomatitis and fatigue) of grade 3, S-1 was stopped until recovery. If patients had counts of leukocytes $<2000/mm^3$, platelets $<50\,000/mm^3$, total bilirubin >1.5 mg/dl, AST or ALT levels >100IU/l or non-haematological toxicity (nausea, vomiting, diarrhoea, stomatitis and fatigue) of grade 3, docetaxel was stopped until recovery; however, if these toxicities lasted for more than 14 days, docetaxel was skipped. To receive a subsequent cycle of chemotherapy, patients had to have leukocyte counts $>3000/mm^3$, neutrophil counts $>1500/mm^3$, platelets $>100\,000/mm^3$ and serum creatinine <1.2 mg/dl, and the recovery of any treatment-related non-haematological toxicity to grade <1 (except alopecia and neuropathy). Treatment was repeated until disease progression, patient refusal, a serious adverse event occurred or completion of the protocol-designated treatment of eight cycles.

Dose-Limiting Toxicity

A DLT was defined as any of following events observed before the second course: (i) grade 4 neutropenia lasting for >3 days, even with granulocyte colony stimulating factor; (ii) grade 3 febrile neutropenia; (iii) grade 4 thrombocytopenia; (iv) grade 3 or 4 non-haematological toxicity (excluding nausea, vomiting, constipation, allergic reaction and electrolyte abnormalities); (v) grade 3 diarrhoea persisting despite adequate anti-diarrhoeal medication; (vi) a delay of starting the second course over 2 weeks; (vii) skipping docetaxel administration (day 8 or 15) or (vii) the interruption of S-1 medication >7 days.

Toxicity and Response Evaluation

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0. Patients' symptoms and general condition were observed periodically, and physical examinations, complete blood counts with differential counts, and serum chemical laboratory and urine tests were checked at least once a week during the DLT evaluation period. Tumour response was evaluated according to RECIST version 1.0 (18) every 2 months until tumour progression. Progression-free survival was defined as the time from the date of starting treatment to the date of the first documentation of disease progression (by imaging methods or clinical judgment) or death. Patients with progression-free status were censored at the last date verifying survival. Overall survival was defined as the time from the date of starting treatment to the date of death. Surviving patients were censored at the last confirmation date of survival.

This phase I study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at Shizuoka Cancer Center and Aichi Cancer Center, including the protocol amendment. An independent data and safety monitoring committee monitored this study. The study was registered with UMIN-CTR, number UMIN000000978.

RESULTS

Fifteen patients were enrolled in this study between September 2007 and March 2009 at Shizuoka Cancer Center and Aichi Cancer Center. Toxicity was assessable in all patients, and objective response was assessable in 13 patients with target lesions. The patient characteristics are shown in Table 1. The patients' median age was 65 (range, 52–72) years; three patients (20%) had prior gastrectomy, and three (20%) and two patients (13%) had prior chemotherapy in the neo-adjuvant and adjuvant settings, respectively. A total of 67 cycles of chemotherapy were administered with a median of 4 cycles. One patient was lost to follow-up because of moving to another hospital after discontinuation of treatment.

Toxicity

Major adverse events occurring during the first cycle at each DL are shown in Table 2. There was no DLT at DL1 and DL2. Grade 3 febrile neutropenia occurred in one of the three patients at DL3. At DL4, two DLTs, grade 3 infection in one patient with a normal absolute neutrophil count (blood) and grade 3 pain (abdomen-NOS) in another patient were observed. In the former patient, who had peritoneal metastasis, fever (40°C) was observed on day 3 after initiation of chemotherapy, and antibiotics were administered after performing the blood culture. Thereafter, his body temperature was reduced on day 5. The result of a blood culture showed gram-negative bacillus, and we defined this adverse event as a DLT, because it is very difficult to deny the relation between this event and the protocol treatment.

Table 1. Patient characteristics

Characteristics	*n* (%)
Patients enrolled	15 (100)
Sex	
Male	11 (73)
Female	4 (27)
Age	
Median (range)	65 (52–72) years
ECOG PS	
0	11 (73)
1	4 (27)
Histological type	
Intestinal	8 (53)
Diffuse	7 (47)
Prior surgery	
None	12 (80)
Gastrectomy	3 (20)
Prior chemotherapy	
Neo-adjuvant	1 (7)
Adjuvant	2 (13)
None	12 (80)
Site of metastasis	
Lymph node	13 (87)
Liver	4 (27)
Peritoneum	4 (27)
Lung	2 (13)
Pleura	2 (13)
Navel	1 (7)
No. of metastasis sites	
0	5 (33)
1	7 (47)
2	3 (20)
Target lesion	
Present	13 (87)
Absent	2 (13)

ECOG, Eastern Clinical Oncology Group.

In the latter case, grade 3 abdominal pain occurred on day 13 after the initiation of chemotherapy, after which the administration of S-1 was discontinued and patient was taken off food, with the administration of pentazocine hydrochloride if necessary. The patient recovered from pain on day 17, and this adverse event was thought to be enteritis related to S-1.

From these results, we determined that the MTD of this triplet regimen was DL4.

Toxicities in all treatment cycles are shown in Table 3. As anticipated, myelosuppression was the major toxicity of this regimen. However, there was no episode of febrile neutropenia, although one patient with a normal neutrophil count experienced infection. As for the non-haematological toxicities, grade 3 fatigue was seen in one patient each at DL1, DL2 and DL3, and anorexia in one patient at DL2 and DL3, which led to a protocol amendment. Among the six patients at DL4, grade 4 haematological toxicity did not occur, grade 3 nausea occurred in one patient, grade 3 anorexia in two patients and grade 3 hyponatremia in one patient.

One patient at DL1 died within 30 days after the last administration of the treatment according to protocol. This patient received gastro-jejunostomy for impaired gastric passage because of progressive disease on day 32 in the sixth cycle of the protocol treatment, and then experienced sepsis and multiple organ dysfunction.

Table 2. Adverse events during the first cycle

	Dose level 1 ($n = 3$)				Dose level 2 ($n = 3$)				Dose level 3 ($n = 3$)				Dose level 4 ($n = 6$)			
	Grade				Grade				Grade				Grade			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Haematological																
Leukocytes	1	1	0	0	0	2	0	0	0	0	2	0	0	4	1	0
Neutrophils	0	2	0	0	0	1	1	0	0	0	2	0	0	1	3	0
Haemoglobin	2	1	0	0	1	1	1	0	0	3	0	0	1	4	1	0
Platelets	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
Non-haematological																
Nausea	1	0	0	0	0	2	0	0	1	1	0	0	0	1	1	0
Vomiting	0	0	0	0	1	1	0	0	2	0	0	0	1	1	0	0
Anorexia	1	1	0	0	2	1	0	0	1	2	0	0	2	1	2	0
Fatigue	3	0	0	0	0	2	0	0	1	2	0	0	3	0	0	0
Diarrhoea	1	0	0	0	1	0	0	0	1	0	0	0	1	1	0	0
Stomatitis	2	1	0	0	0	2	0	0	0	0	0	0	0	1	0	0
Febrile neutropenia	–	–	0	0	–	–	0	0	–	–	1	0	–	–	0	0
Infection	–	0	0	0	–	0	0	0	–	0	0	0	–	0	1	0
Abdominal pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Efficacy

Response was evaluated in 13 patients who had target lesions. Objective tumour responses at each DL are shown in Table 4. Of the 13 patients with target lesions, seven patients (two at DL1; three at DL2; one at DL3; one at DL4) achieved partial responses yielding an overall response rate of 54% [95% confidence interval (CI), 27–81%]. Median progression-free survival was 243 days, and median overall survival was 383 days with a median follow-up period of 290 days.

Table 3. Adverse events in all cycles

	Dose level 1 ($n = 3$)				Dose level 2 ($n = 3$)				Dose level 3 ($n = 3$)				Dose level 4 ($n = 6$)			
	Grade				Grade				Grade				Grade			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Haematological																
Leukocytes	0	1	1	0	0	0	3	0	0	0	3	0	0	3	2	0
Neutrophils	0	1	1	0	0	0	3	0	0	0	1	2	1	1	3	0
Haemoglobin	2	0	1	0	1	0	2	0	1	1	0	1	1	4	1	0
Platelets	0	0	0	0	0	0	0	0	1	2	0	0	1	0	0	0
Non-haematological																
Nausea	1	0	0	0	0	0	0	0	0	1	0	0	1	2	1	0
Vomiting	1	0	0	0	1	1	0	0	2	0	0	0	1	2	0	0
Anorexia	0	2	0	0	0	2	1	0	0	2	1	0	3	1	2	0
Hyponatremia	2	–	0	0	1	–	2	0	2	–	1	0	2	–	2	0
Fatigue	1	1	1	0	0	2	1	0	0	2	1	0	1	3	0	0
Diarrhoea	1	2	0	0	0	1	0	0	1	0	0	0	0	3	0	0
Stomatitis	2	1	0	0	0	2	0	0	1	1	0	0	1	2	0	0
Febrile neutropenia	–	–	0	0	–	–	0	0	–	–	1	0	–	–	0	0
Infection	–	0	0	0	–	0	1	0	–	0	0	0	–	0	1	0
Haemorrhage	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Table 4. Response rate

Dose level	Number of patients	Total number of cycles administered	Overall response					RR (%)
			CR	PR	SD	PD	NE	
1	3	16	0	2	1	0	0	67
2	3	15	0	3	0	0	0	100
3	3	13+	0	1	0	2	0	33
4	4	12+	0	1	0	2	1	25
Total	13	56+	0	7	1	4	1	54

CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; NE, not evaluated; RR, response rate.

Reason of Protocol Treatment Cessation

In October 2009, protocol treatment was continued in three patients. The reasons for discontinuation of the protocol treatment were progressive disease in seven (47%), patient refusal due to toxicities in three (20%, severe fatigue in two and abdominal pain in one) and completion of eight cycles of protocol treatment in two (13%) patients. One patient, who had only para-aortic lymph node metastasis, had completed eight cycles of treatment and had a partial response. Thereafter, he received gastrectomy and lymphadenectomy with curative intent. The pathological findings showed only 1 of 36 dissected lymph nodes with small nests of metastasis, and no residual tumour was detected in the primary site.

DISCUSSION

Several reports showed the superiority of triplet chemotherapy containing a taxane compared with doublet chemotherapy with fluorouracil plus cisplatin for head and neck cancer (20,21) and gastric cancer (2). However, high incidences of severe neutropenia and febrile neutropenia are serious problems associated with these treatment regimens. Recently, triplet regimens with divided-dose docetaxel have been investigated. Tebbutt et al. (22) reported a randomized phase II trial (AGITG ATTAX). In this study, the schedule of this triplet (weekly TCF) regimen included weekly administration of docetaxel as follows: docetaxel 30 mg/m^2 on days 1 and 8, cisplatin 60 mg/m^2 on day 1 and fluorouracil 200 mg/m^2 continuously every three weeks. The incidence of febrile neutropenia was 4%. Another phase II study of a triplet regimen with a bi-weekly dose of docetaxel was the GASTRO-TAX-1 trial (23). The schedule of the T-PLF regimen was docetaxel 50 mg/m^2 and cisplatin 50 mg/m^2 on days 1, 15 and 29, and fluorouracil 2000 mg/m^2 plus leucovorin 500 mg/m^2 on days 1, 8, 15, 22, 29 and 36 every 8 weeks. The incidence of febrile neutropenia was also as low as 5%. In this study of DCS with divided-dose docetaxel, none of the 15 patients experienced febrile neutropenia, although some haematological toxicity occurred. Thus, divided-dose docetaxel added to a cisplatin plus fluorouracil regimen is associated with lower grade haematological toxicities than triplet chemotherapy based on thrice-weekly docetaxel.

A weekly schedule of docetaxel has been investigated in several cancers such as lung, breast and prostate cancer. A review of randomized studies (19), which compared weekly versus thrice-weekly administration of docetaxel, reported that the efficacy appeared to be similar between the two schedules in all diseases. However, severe fatigue and asthenia were the most common non-haematological toxicities in patients treated with a weekly schedule of docetaxel. In our study, two patients refused protocol treatment because of severe fatigue, causing us to amend the protocol to add DL4, which included a bi-weekly schedule of docetaxel. The results of this study show that fatigue greater than grade 3 was observed at all DLs (DL1, DL2 and DL3) with a weekly schedule of docetaxel; however, severe fatigue was not seen at DL4 with bi-weekly docetaxel. Although the follow-up period was shorter in the DL4 cohort than at the other DLs, bi-weekly docetaxel seemed to be better tolerated than docetaxel administered weekly.

Two different schedules of combination regimens with docetaxel, cisplatin and S-1 (DCS regimen) for advanced or recurrent gastric cancer are reported in Japan. Sato et al. (24)

reported on a phase II study of the DCS regimen, which consisted of S-1 (40 mg/m^2 b.i.d.) on days 1–14, intravenous cisplatin (60 mg/m^2) and docetaxel (60 mg/m^2) on day 8 every 3 weeks. The objective response rate was 87.1% with onecomplete response (3.2%); the median survival time and progression-free survival were 687 days and 226 days, respectively, and the regimen was associated with severe haematological toxicities. Nakayama et al. (25) reported on another phase II study of the DCS regimen, which consisted of docetaxel (40 mg/m^2) and cisplatin (60–70 mg/m^2) given intravenously on day 1, and S-1 given orally at a dose of 40 mg/m^2 twice daily from days 1 to 14 of a 28-day cycle. The overall response rate was 81.3% (48/59; 95% CI, 80.7–91.2), and the median survival time and progression-free survival had not been reached. From the results of these two phase II studies, the response rates of triplet regimens were estimated to be around 80%. These phase II studies suggested that triplet chemotherapy regimens using S-1 might be more active than those with 5-FU.

In the future, DCS regimens are likely to have two indications: as palliative care and in the neo-adjuvant setting; and triplet regimens at higher dose intensities are anticipated to be suitable for maximizing tumour shrinkage in the neo-adjuvant setting. On the other hand, less toxic regimens seem to be preferred in the palliative setting. It is necessary to select the most suitable regimens in both the neo-adjuvant and palliative settings by comparing these triplet regimens from the comprehensive view of the response rate (water-fall plot), progression-free survival, time to treatment failure and adverse events. Because the sample size of this study was very small, the triplet regimen with bi-weekly doses of taxane, which can maintain high dose intensity, will require further investigation in a suitable treatment setting.

In conclusion, the RD of the DCS regimen is as follows: docetaxel 40 mg/m^2 on days 1 and 15, cisplatin 60 mg/m^2 on day 1, S-1 80 mg/m^2 on days 1–21 every 5 weeks. Divided-dose docetaxel could be added to a standard dose of S-1 plus cisplatin combination therapy for advanced gastric cancer.

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Conflict of interest statement

None declared.

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Original article

Safety and efficacy of S-1 monotherapy in elderly patients with advanced gastric cancer

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Abstract

Background. **Although S-1 is effective against advanced gastric cancer (AGC), its efficacy in elderly patients has not yet been investigated sufficiently. We assessed the efficacy and safety of S-1 monotherapy in elderly patients with AGC.**

Methods. **We conducted a retrospective review of the data of 153 patients with unresectable/recurrent gastric adenocarcinoma who received S-1 monotherapy as first-line chemotherapy at our institution. S-1 was administered orally twice daily at the dose of 40 mg/m^2, on days 1–28, every 6 weeks. We categorized the patients into three groups, the young (≤65 years old), the middle-aged (66–75 years old), and the elderly (≥76 years old); and the drug toxicity, objective responses, progression-free survivals, and overall survivals were compared among the three groups.**

Results. **The incidence of leukopenia of grade 3 or greater in the three groups was 7%, 5%, and 13%, and that of anemia was 9%, 18%, and 27%, respectively. In regard to nonhematological toxicities, the incidence of nausea of grade 3 or greater was 3%, 5%, and 13%; that of fatigue was 5%, 11%, and 20%; and that of anorexia was 5%, 6%, and 27%, respectively. As for the treatment efficacy, the objective response rates, median progression-free survivals, and overall survivals in the young, middle-aged, and elderly groups were 53%, 46%, and 33%; 7.8, 5.6, and 3.9 months; and 16.9, 17.1; and 7.7 months, respectively.**

Conclusion. **Although S-1 monotherapy showed moderate efficacy in elderly (≥76 years) patients with AGC, patients in this age group showed higher incidences of severe toxicities than the younger patients.**

Key words S-1 · Elderly · Gastric Cancer · Safety · Efficacy

Introduction

Gastric cancer is the second leading cause of death from malignant disease in the world [1, 2]. In Japan, gastric cancer is the most frequently encountered malignancy and the second leading cause of cancer-related death [3]. The prognosis of unresectable or recurrent tumors is very poor: the median survival time is about 4 months with best supportive care [4–6]. Although several randomized trials of treatments for advanced gastric cancer were conducted during the 1990s, with anthracyclines, mitomycin C, 5-fluorouracil (5-FU), methotrexate, and cisplatin [7–15], no standard treatment for advanced gastric cancer was established.

S-1 is an oral fluoropyrimidine, consisting of tegafur (a prodrug of fluorouracil), 5-chloro-2, 4-dihydropyrimidine (CDHP), and potassium oxonate. CDHP is an inhibitor of dihydropyrimidine dehydrogenase (DPD), which is the rate-limiting enzyme for the degradation of fluorouracil [16]. Three randomized controlled trials of S-1 monotherapy have been reported from Japan. One was the Japan Clinical Oncology Group (JCOG) 9912 trial, which showed the noninferiority of S-1 to continuous infusion of 5-FU, adopted as the reference arm for patients with unresectable or recurrent gastric cancer, based on the result of the JCOG9205 trial [15, 17]. The second trial was the S-1 plus cisplatin versus S-1 in RCT in the treatment for stomach cancer (SPIRITS) trial, conducted in 2007, which showed the superiority of S-1 plus cisplatin to S-1 alone in patients with advanced gastric cancer [18]. The third trial was the randomized phase III study of irinotecan plus S-1 (IRIS) versus S-1 alone as first-line treatment for advanced gastric cancer (GC0301/TOP-002), which did not demonstrate the superiority of S-1 plus irinotecan (CPT-11) to S-1 alone [19]. From the results of these three phase III trials, S-1 plus cisplatin came to be recognized as the standard of care for patients with advanced gastric cancer in Japan, while S-1 monotherapy was a community standard until 2007.

In recent years, the percentage of elderly people in the general population in Japan has increased remarkably, to more than 20%, owing to the prolonged lifespan of the

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Japanese. Considering this social background, chemotherapy for elderly cancer patients is an important issue that must be addressed. However, because gastric cancer patients who were more than 75 years old were not included in the three aforementioned Japanese phase III trials, elderly patients are generally administered monotherapy with S-1, which is not as intensive as S-1 plus cisplatin. However, the efficacy and toxicity of S-1 monotherapy in elderly patients has not yet been clarified.

In this study, we assessed the safety and efficacy of S-1 monotherapy as a function of the age of patients with advanced gastric cancer.

Subjects, materials, and methods

Patients

The subjects were patients with unresectable or recurrent gastric cancer who received S-1 monotherapy at our hospital. The patient selection criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; histologically proven adenocarcinoma; no previous history of chemotherapy; adequate oral intake; adequate bone marrow, renal, and hepatic functions (defined as an absolute neutrophil count of ≥1500/μl, hemoglobin of ≥8.0 g/dl, serum creatinine of ≤1.5 mg/dl, serum transaminase levels less than threefold the upper limit of normal); and no concomitant malignancy. The presence of measurable lesions was not mandatory.

We categorized the patients into three groups, as follows; the young group (less than 66 years old), the middle-aged group (66 years or older, but not older than 75 years), and the elderly (more than 75 years old).

Treatment dose and schedule

S-1 was administered orally twice daily at the dose of 40 mg/m^2 from day 1 to day 28, followed by 14 days' rest, and this regimen was repeated every 42 days until disease progression, the appearance of unacceptable toxicities, or the patient's refusal to continue treatment. The dosage of S-1 was determined according to the body surface area (BSA), as follows: BSA less than 1.25 m^2, 40 mg bid; BSA 1.25 to 1.5 m^2, 50 mg bid; BSA more than 1.5 m^2, 60 mg bid. We suspended treatment during the cycle or delayed the treatment cycle until nonhematological toxicities recovered to grade 1 or lower, the neutrophil count was 1500/μl, and the platelet count was 7.5×10^4/μl. The dose of S-1 was reduced by 20% (level 1) in the event of any of the following occurrences during the previous cycle: grade 4 decrease in the leukocyte count, hemoglobin, or platelet count; and/or grade 3 or higher nonhematological toxicities. If these toxicities appeared again at the reduced dose, an additional reduction of the dose of S-1 by 20% (level 2) was made. The treatment schedule of 2 weeks' administration every 3 weeks was permitted if severe adverse events were seen after the second week in each course. A dose reduction of S-1 by one level at the initiation of the therapy was also permitted considering the patient's age, PS, and organ functions.

Response and toxicity evaluation

We obtained all the clinical data from the medical records retrospectively. We repeated physical examinations and laboratory tests at least once every 2 weeks. Objective response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0, and toxicity was evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Statistical analysis

Overall survival (OS) was defined as the period from the date of the first administration of S-1 to the date of death from any cause or the last date on which the patient was confirmed to be alive. Progression-free survival (PFS) was defined as the period from the date of the first administration of S-1 to the date of confirmation of tumor progression by imaging, or the date of symptomatic deterioration by clinical judgment, or the last date on which the patient was confirmed to be alive without disease progression. Patients who had only the one noncurative factor of positive peritoneal washing cytology were excluded from the PFS and OS analyses, because it was suggested that these patients would survive longer than patients with other noncurative factors; however these patients' toxicities were assessed. Patients who did not have target lesions were also excluded from the response rate (RR) analysis. The survival curves were calculated by the Kaplan-Meier method, using StatView, version 5.0 (Abacus Concepts, Berkeley, CA, USA). Written informed consent was obtained from each of the patients prior to their starting the chemotherapy.

Results

Patient characteristics

A total of 165 patients received S-1 monotherapy between September 2002 and October 2007. Of these, 12 patients were excluded, for the following reasons: hepatic function disorder (5 patients), concomitant malignancy (3 patients), severe anemia (2 patients), renal failure (1 patient), and massive pleural effusion and/or ascites (1 patient).

Table 1. Patient characteristics at baseline

		Young (n = 76)	Middle-aged (n = 62)	Elderly (n = 15)	P value
Age (years)	Median	59.5	70	77	<0.0001
	(range)	(34–65)	(66–75)	(76–80)	
Sex	Male	52	49	10	0.33
	Female	24	13	5	
PS	0	43	26	4	0.02
	1	32	35	8	
	2	1	1	3	
Tumor status	Unresectable	59	54	14	0.18
	Recurrent	17	8	1	
CCr (ml/min)[a]	Median	88.3	65.4	59.9	<0.0001
	(range)	(35.5–143.7)	(35.9–104.9)	(41.3–93.9)	
Macroscopic type	1	0	2	2	0.16
	2	19	16	7	
	3	35	32	2	
	4	20	9	4	
	Unknown	2	3	0	
Histological type	Intestinal	15	26	8	0.01
	Diffuse	60	32	7	
	Unknown	1	4	0	
No. of metastatic sites	1	54	28	5	0.003
	2	18	31	7	
	≥3	4	3	3	
Target lesions	+	32	35	12	0.02
	–	44	27	3	
Noncurative factors	Only CY1	20	12	1	0.21
	Others	56	50	14	

The P values were determined using the Kruskal-Wallis test
PS, performance status; CCr, creatinine clearance; CY1, positive peritoneal washing cytology
[a]Cockcroft-Gault equation

The baseline characteristics of the patients in the three groups are shown in Table 1. The median age was 59.5 years (range, 34 to 65 years) in the young group, 70 years (range, 66 to 75 years) in the middle-aged group, and 77 years (range, 76 to 80 years) in the elderly group. The percentage of patients with PS 2 was higher (20%) in the elderly group than in the other two groups. The median creatinine clearance (calculated by the Cockcroft-Gault equation) was 88.3 ml/min in the young group, 65.4 ml/min in the middle-aged group, and 59.9 ml/min in the elderly group. There were 32 (42%), 35 (56%), and 12 (80%) patients with target lesions, and 20 (26%), 12 (19%), and 1 (6%) patients with positive peritoneal washing cytology as the only noncurative factor in the young, middle-aged, and elderly groups, respectively.

Exposure to treatment

The median number of treatment cycles was 5.5 (range, 1 to 28) in the young group, 5 (range, 1 to 18) in the middle-aged group, and 3 (range, 1 to 13) in the elderly group. Dose reduction of S-1 was required in some patients in all three groups: in 12 patients (16%) in the young group, 14 patients (23%) in the middle-aged group, and 8 patients (53%) in the elderly group. Delay of the subsequent treatment cycle was also necessitated in some patients in all three groups: in 23 patients (30%) in the young group, 26 patients (42%) in the middle-aged group, and 5 patients (33%) in the elderly group.

The median relative dose intensity (RDI) per patient in the elderly group was only 75.8%, whereas the corresponding values in the young and middle-aged groups were 99.5% and 96.3%. In 7 (47%) of the 15 patients in the elderly group, S-1 was administered at a reduced dose from the start, and in 8 patients in the elderly group (53%), the dose of S-1 was reduced due to the appearance of toxicity during the treatment courses, and 3 of these 8 patients needed additional dose reduction because of the development of severe adverse events.

The reasons for treatment discontinuation are shown in Table 2. The most frequent reason in all three groups was disease progression. While two patients in the young group required treatment discontinuation because of the development of adverse events (grade 3 pneumonitis in one, and grade 2 skin rash in the other), none of the patients in the elderly group required treatment

Table 2. Reasons for treatment discontinuation

	Young (n = 76)	Middle-aged (n = 62)	Elderly (n = 15)
S-1 discontinuation	74 (97%)	62 (100%)	15 (100%)
Disease progression	60	52	13
Adverse events	2	0	0
Patient's refusal	0	3	0
Lost to follow-up	1	1	1

Table 3. Adverse events

	Young (n = 76)				Middle-aged (n = 62)				Elderly (n = 15)				
	G1/2	G3	G4	≥G3 (%)	G1/2	G3	G4	≥G3 (%)	G1/2	G3	G4	≥G3 (%)	P value
Hematological													
Leukopenia	41	5	0	7	36	3	0	5	3	2	0	13	0.28
Neutropenia	26	10	1	14	25	5	0	8	2	2	0	13	0.45
Anemia	63	7	0	9	51	10	1	18	9	4	0	27	0.08
Thrombocytopenia	21	1	0	1	15	1	0	2	6	0	0	0	0.59
Nonhematological													
Nausea	28	2	0	3	16	3	0	5	7	2	0	13	0.08
Vomiting	16	0	0	0	9	0	0	0	5	0	0	0	0.24
Anorexia	40	4	0	5	34	4	0	6	8	4	0	27	0.07
Diarrhea	29	0	0	0	16	0	0	0	5	0	0	0	0.31
Mucositis	25	1	0	1	22	4	0	6	6	0	0	0	0.53
Fatigue	19	4	0	5	21	7	0	11	8	3	0	20	0.004
Febrile neutropenia	—	0	0	0	—	0	0	0	—	0	0	0	
Death within 30 days				0				0				1	

The P values were determined using the Kruskal-Wallis test

discontinuation because of adverse events or the patient's refusal.

Adverse events

Table 3 shows the adverse events until 30 days from the last administration of S-1 or the day of initiation of second-line treatment, whichever was earlier. The incidences of grade 3/4 decreases in the leukocyte count and serum hemoglobin were 7% and 9% in the young group, 5% and 18% in the middle-aged group, and 13% and 27% in the elderly group, respectively. One patient in the middle-aged group showed a grade 4 decrease in serum hemoglobin, and one patient in the young group showed grade 4 neutropenia. In regard to the nonhematological toxicities, the incidences of grade 3/4 nausea, anorexia, and fatigue seemed to be higher in the elderly group than in the other two groups. Thus, it would appear that patients in the elderly group experienced more severe hematological and nonhematological toxicities than those in the young and middle-aged groups, while the incidences of toxicities were similar in the young and middle-aged groups. One patient in the elderly group died within 30 days from the last administration of S-1. He was 80 years old, with PS 2, and the estimated creatinine clearance was 56 ml/min at the baseline. He received S-1 administration at a reduced dose even from the first cycle because of his advanced age and anorexia caused by primary cancer. When he visited our hospital on day 17, he was found to have grade 2 mucositis. On day 23, he was admitted to another hospital because of severe anorexia and fatigue, and received some infusion therapy. However, he died on day 30 after the last administration of S-1. The attending physician judged that the cause of death was disease progression.

Response and survival

Among the patients with target lesions, the RR was 53% (17/32) in the young group, 46% (16/35) in the middle-aged group, and 33% (4/12) in the elderly group. Two patients (6%) in the middle-aged group showed a complete response (CR).

The data of 56 patients in the young group, 50 in the middle-aged group, and 14 in the elderly group were analyzed in the calculations of the PFS and OS. The median PFS values in the young group, middle-aged group, and elderly group were 7.8 months, 5.6 months, and 3.9 months (Fig. 1), and the median overall survivals

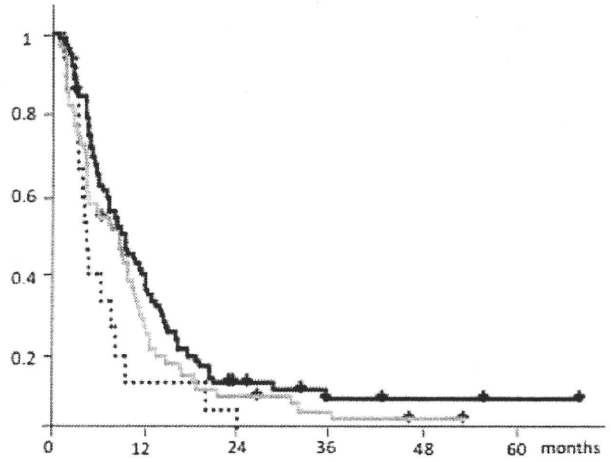

Fig. 1. The median progression-free survival (PFS) was 7.8 months in the young group (*solid line*), 5.6 months in the middle-aged group (*faint line*), and 3.9 months in the elderly group (*dotted line*)

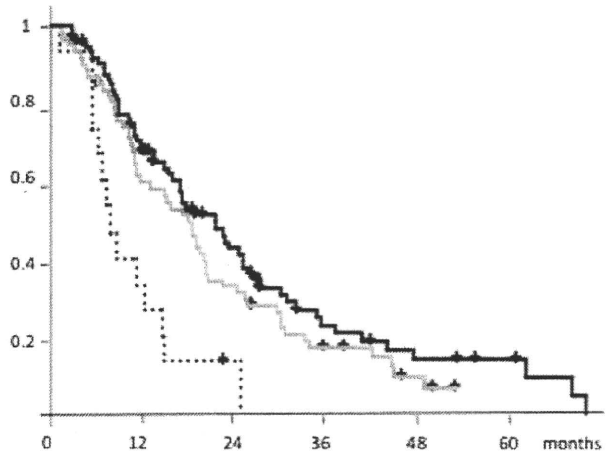

Fig. 2. The median OS was 16.9 months in the young group (*solid line*), 17.1 months in the middle-aged group (*faint line*), and 7.7 months in the elderly group (*dotted line*)

in the three groups were 16.9 months, 17.1 months, and 7.7 months, respectively (Fig. 2). It would seem that the treatment efficacy in the elderly group was inferior to that in the other two groups, while the young and middle-aged groups showed similar treatment efficacy.

Discussion

It still remains under debate whether standard chemotherapies established by pivotal phase III trials might also be applicable to elderly patients with advanced gastric cancer [20–23]. Lee et al. [24] conducted a randomized phase II study comparing capecitabine and S-1 in patients older than 65 years, and showed satisfactory efficacy of S-1 (RR, 29%; median time to progression, 4.2 months; median OS, 8.1 months). In Japan, Koizumi et al. [25] conducted a phase II study of S-1 in patients older than 75 years and demonstrated a RR of 21%, median PFS of 3.9 months, and median OS of 15.7 months. Similar results were obtained in the elderly group in the present study. Because these results are consistent with those of the previous phase III studies in Japan [17–19] (RR of about 30% and PFS of about 4 months), it is considered that S-1 monotherapy may be effective in elderly patients with gastric cancer.

However, elderly cancer patients often have comorbidities and age-related physiological problems, such as organ dysfunction. The kidney is a very common route for the excretion of drugs; however, it is reported that the glomerular filtration rate generally decreases by approximately 0.75 ml/min per year after the age of 40, on average [26]. In several pharmacokinetic studies of chemotherapeutic drugs, such as paclitaxel, vinorelbine, etoposide, cisplatin, and doxorubicin, an age-related decrease in creatinine clearance has been reported [23].

Lee et al. [24] and Koizumi et al. [25] reported the following incidences of grade 3/4 toxicities: decrease in serum hemoglobin, 9%–14.3%; anorexia, 9.5%–12%; and nausea, 4.8%–6%. These data are similar to those in the middle-aged group in the present study (decrease in serum hemoglobin, 18%; anorexia, 6%; nausea, 5%). In the elderly group in the present study, the incidences of severe toxicities (decrease in serum hemoglobin, 27%; anorexia, 27%; nausea, 13%) were higher than those reported from the previous trials, despite about half of our elderly patients having received S-1 at a reduced dose from the first administration. The conditions of patients in daily clinical practice are generally worse than those in patients participating in clinical trials. Actually, in the present study, the median creatinine clearance, estimated by the Cockcroft-Gault equation, was lower in the elderly group (59.9 ml/min) than the values in the middle-aged (65.4 ml/min) and younger (88.3 ml/min) groups. It is known that the clearance of CDHP is reduced by renal dysfunction, resulting in a high blood concentration of 5-FU due to decreased DPD activity [27, 28]. In a post-marketing survey of S-1, it was reported that the incidence of toxicities was greater in patients with renal dysfunction than in those with normal renal function [29]. Thus, it is considered that renal dysfunction is the main reason for the high incidence of severe S-1 toxicities in elderly patients. Therefore, careful evaluation of the renal function prior to the initiation of S-1 monotherapy is strongly recommended.

In conclusion, in the present study, although S-1 monotherapy exhibited moderate efficacy in elderly

patients (≥76 years of age) with advanced gastric cancer, this subject population is at a higher risk of severe toxicities than the other two age groups (66–75 years old and younger) examined in this study. Careful monitoring of renal function and toxicities during treatment is recommended, especially in elderly patients.

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Development of pancreatic cancers during long-term follow-up of side-branch intraductal papillary mucinous neoplasms

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Background and study aims: Side-branch intraductal papillary mucinous neoplasms (SB-IPMNs), and associated synchronous and metachronous pancreatic cancers are increasingly detected as imaging modalities become more sensitive. We investigated the natural history of SB-IPMN, and the incidence and characteristics of pancreatic cancers among patients undergoing long-term follow-up.

Patients and methods: We reviewed the clinical, imaging, and pathological features in 103 patients, diagnosed at the Aichi Cancer Center between September 1988 and September 2006 as having SB-IPMN, and conservatively followed up for ≥ 2 years (median 59 months) based on an endoscopic ultrasonography (EUS) database.

Results: 74 (71.8%) patients had nonprogressive lesions. Overall, six patients (5.8%) developed pancreatic cancers during follow-up, with intraductal papillary mucinous (IPM) carcinoma in four, and ductal carcinoma of pancreas that was not IPMN in two patients. Of the six pancreatic cancers, five were diagnosed at a resectable stage. The 5-year and 10-year actuarial rates of development of pancreatic cancer were 2.4% and 20.0%, respectively. Although, at the last follow-up, cyst size, main pancreatic duct (MPD) diameter, mural nodule size, and frequency of metachronous and/or synchronous cancers of other organs were significantly higher in patients who developed IPM carcinoma, resected SB-IPMNs without mural nodules and dilated MPDs had no IPM carcinomas.

Conclusions: The frequency of pancreatic cancers is high on long-term follow-up of SB-IPMN. Although conservative management is appropriate for selected patients, regular and long-term imaging, especially by EUS is essential, even if SB-IPMN remains unchanged for 2 years. Presence of mural nodule and dilated MPD seem to be more appropriate indicators for resection than cyst size alone for SB-IPMNs.

Introduction

Since its first description by Ohhashi et al. in 1982 [1], the reported incidence of intraductal papillary mucinous neoplasms (IPMNs) has been increasing, partly because of growing awareness about them and wider application of sensitive imaging tests. Diagnostic criteria for IPMN have been established, but no consensus exists regarding optimal treatment protocols [2–8]. In 2006, the International Association of Pancreatology (IAP) guidelines for managing IPMN of the pancreas suggested treatment protocols [9], but several controversies still remain.

Most studies detailing the natural history of IPMN have been surgical, and have reported a high prevalence of carcinoma. Malignancy (in situ and invasive) has been identified worldwide in 70% and 25% of resected main pancreatic duct IPMNs, and side-branch IPMNs (SB-IPMNs), respectively [9]. There is an emerging consensus that IPMN is a premalignant condition, with an adenoma-to-carcinoma sequence similar to that of colon carcinoma. Furthermore, it is difficult to preoperatively distinguish between benign and malignant IPMN. For these reasons, early resection of all main duct IPMNs and some SB-IPMNs has been advocated [5,9–12], but the indications for resection of SB-IPMN are still controversial. In addition, synchronous or metachronous development of ductal cancers of the pancreas other than SB-IPMNs has been recently reported in these patients [13–16]. The prognosis for patients with noninvasive IPMN is excellent, whereas that for patients with invasive IPMN or ductal cancer of the pancreas is significantly inferior [17,18]. Hence, we believe that the long-term prognosis of patients with SB-IPMN depends on whether or not pancreatic cancer supervenes in these patients.

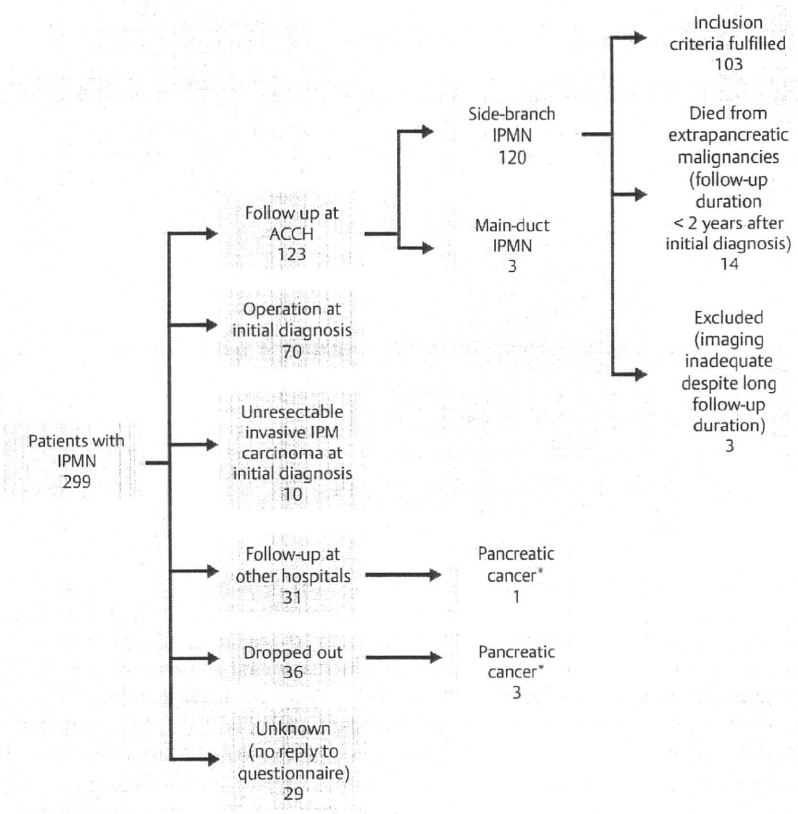

Fig. 1 Inclusion and exclusion of patients with side-branch intraductal papillary mucinous neoplasms (IPMNs) in follow-up study. *These four pancreatic cancers were reported by questionnaire, so we could not tell whether they were ductal carcinoma of the pancreas or intraductal papillary mucinous carcinoma. ACCH, Aichi Cancer Center Hospital.

In the present study, we investigated the frequency of pancreatic cancers found on long-term follow-up among patients with SB-IPMN, the characteristics of these cancers, and the optimal follow-up protocols.

Patients and methods

A review of the database of endoscopic ultrasonography (EUS) procedures performed at Aichi Cancer Center Hospital (ACCH), Nagoya, Japan, between September 1988 and September 2006, revealed a total of 299 patients with IPMN. The inclusion criteria for the present study were: presence of SB-IPMN, a minimal follow-up duration at ACCH of 2 years at September 2008, and availability of findings from serial imaging and of clinical details.

Of the 299 patients, 70 underwent surgery, and another 10 were found to have unresectable IPMC at their initial diagnosis, 31 underwent follow-up at other hospitals, 36 dropped out from follow-up in ACCH or other hospitals, and the final status of 29 was unknown because of failure to reply to the study questionnaire mentioned below (see **Fig. 1**).

Among those who were followed up at other hospitals and those who eventually dropped out, pancreatic cancers (ductal carcinomas of the pancreas, or invasive intraductal papillary mucinous [IPM] carcinomas) developed in 4 of 67 patients. We obtained data from the referring hospitals through a clinical questionnaire that had been approved by the Ethical Committee of the ACCH.

The remaining 123 patients underwent follow up at ACCH. These 123 patients included three patients with main pancreatic duct (MPD) IPMNs (one rejected the option of surgery, and two underwent conservative follow up because of advanced age and poor clinical status), and 120 patients with SB-IPMNs. Of the latter 120 patients, 14 died due to an extrapancreatic malignancy (follow-up duration < 2 years after the initial diagnosis), and imaging was inadequate in three despite a long duration of follow-up; these 17 patients were excluded from the analysis. The remaining 103 patients fulfilled the inclusion criteria and were evaluated in this study (**Fig. 1**).

SB-IPMNs were defined as cystically dilated side-branch lesions with documented ductal communication, and the presence of mucin identified as filling defects in the main duct or side branch by endoscopic retrograde cholangiopancreatography (ERCP). Patients were diagnosed on the basis of the combined results of ERCP, computed tomographic (CT) scans, magnetic resonance cholangiopancreatography (MRCP), EUS, intraductal ultrasonography (IDUS), and peroral pancreatoscopy (POPS).

The follow-up protocol comprised an at least annual review of all new symptoms and signs, and annual imaging studies, primarily EUS. Initially all EUS studies were done using a mechanical radial echo endoscope, but from 1997 curved linear array echo endoscopy was also used for measuring maximal cyst size, MPD diameter, and mural nodule size during follow-up studies. Solid components, wall thickness, and lymphadenopathy were also noted. Progression of lesions was defined by an increase in the size of the MPD of ≥ 2 mm, of cyst size by ≥ 10 mm, or of mural nodule size by ≥ 1 mm, or the appearance of a pancreatic mass on follow-up imaging. Progression was divided into two categories: higher and lower likelihood of malignancy. Higher likelihood of malignancy was defined as size of mural nodule(s) ≥ 10 mm and/or MPD size of ≥ 10 mm, and/or a rapid increase in size of mural nodule(s) and/or MPD (≥ 5 mm increase since the previous imaging), and/or new appearance of mural nodule(s) in the MPD, and/or the appearance of a pancreatic mass. Progression with lower likelihood of malignancy was defined as an increase in

Age, median (range), years	63 (38 – 84)
Gender, male : female	58 : 45
Follow-up period, median (range), months	59 (24 – 151)
Number of EUS examinations per-patient, median (range), n	5.0 (1* – 14)
Asymptomatic at the initial diagnosis, n (%)	93 (90.3)
Cyst size at the initial diagnosis, median (range), mm	18.0 (4.0 – 50.0)
Presence of mural nodule at initial diagnosis, n (%)	18 (17.5)
Mural nodule size at initial diagnosis, median (range), mm	0.0 (0.0 – 5.0)
Main pancreatic duct diameter at initial diagnosis, median (range), mm	3.0 (1.0 – 7.0)

EUS, endoscopic ultrasonography

* Three patients underwent EUS examination only once; two had further follow-up by ultrasound and computed tomography (CT), and one by endoscopic retrograde cholangiopancreatography (ERCP) and CT.

Table 1 Clinical features in 103 patients with side-branch intraductal papillary mucinous neoplasm (SB-IPMN).

size of the lesions on imaging that did not fulfil the abovementioned criteria.

If there was progression with higher likelihood of malignancy, the patient underwent surgery. In the case of progression with lower likelihood of malignancy, the patient underwent ERCP and CT scan. Those patients in whom cytology detected malignant cells in pancreatic juice underwent surgery, while others were followed up 6 months later. In the case of no progression, we continued annual follow-up.

At our institution, indications for surgery were, as mentioned, progression with higher likelihood of malignancy or cytological detection of malignant cells in pancreatic juice; the presence of significant symptoms (e.g. acute pancreatitis) was another indication. The pathological findings from the resected lesions were reviewed by two pathologists (Y.Y. and A.Y.). Based on the most significant degree of cytoarchitectural atypia, the intraductal components of each tumor were classified as IPMN adenoma, IPMN borderline, IPMN carcinoma in situ (noninvasive IPM carcinoma), or invasive IPM carcinoma, according to the World Health Organization (WHO) classification system [2]. Invasive IPM carcinoma defined according to the WHO system was subclassified into minimally invasive IPM carcinoma and invasive IPM carcinoma, according to the Japan Pancreas Society (JPS) classification [19]. Thus, with the further category of non-IPMN invasive ductal carcinoma of the pancreas, we classified all the tumors into one of six categories.

Statistical analysis

Continuous variables are described using median and range. Patients who developed cancer (noninvasive and invasive) during follow-up were compared with those who remained cancer-free. Intergroup comparisons were done using the χ^2 or Fisher's test for categorical variables, and the Mann-Whitney *U* test for continuous variables. The development rate of pancreatic cancer was estimated using the Kaplan-Meier method. *P* values of < 0.05 were considered significant. Data were statistically analyzed using SPSS software, version 11.0 (SPSS Inc., Chicago, Illinois, USA) and StatView statistical software, version 5.0 (Abacus Concepts Inc, Berkeley, California, USA).

Results

Patient characteristics

The 103 study patients included 58 men (56.3%). The median age of the cohort at the initial diagnosis was 63 years (range 38 – 84). A total of 93 patients (90.3%) were asymptomatic at the initial diagnosis. All patients were followed up for ≥ 2 years, with a median follow-up duration of 59 months (range 24 – 151). Five patients (4.9%) developed symptoms during follow-up. The median number of EUS examinations per-patient during the follow-up period was 5.0 (range 1 – 14). Though three patients underwent EUS examination only once, two of them were followed up using ultrasound and CT, and one using ERCP and CT. At the initial diagnosis, 18 patients (17.5%) had mural nodules.

The median cyst size was 18 mm (range 4.0 – 50.0), median MPD diameter was 3.0 mm (range 1.0 – 7.0), and the median mural nodule was 0.0 mm (range 0.0 – 5.0) in the 103 study patients at the initial diagnosis. The clinical details of the included patients are given in ○ **Table 1**.

Progression of lesions

Progression of lesions, as defined earlier, was monitored by serial EUS studies. A total of 10 SB-IPMNs (9.71%) progressed with higher likelihood of malignancy, 19 (18.45%) progressed with lower likelihood of malignancy, and 74 (71.84%) did not progress (○ **Fig. 2**).

Requirement for surgery and postoperative pathological findings

We operated on 7 of 10 patients who had progressive lesions with higher likelihood of malignancy, 1 of 19 patients with lower likelihood of malignancy, and 3 of 74 patients with nonprogressive lesions (○ **Fig. 2**). Regarding the three patients with higher likelihood of malignancy who did not undergo operation, one was diagnosed as having unresectable invasive IPM carcinoma, one rejected surgery, and one could not have an operation because of respiratory failure. The patient with lower likelihood of malignancy underwent surgery because of recurrent acute pancreatitis. The indications for operation in the three patients with nonprogressive lesions were acute pancreatitis in two patients, and synchronous carcinoid of the papilla in one.

The types of surgery included pancreaticoduodenectomy (n = 6), middle segment pancreatectomy (n = 2), pylorus-preserving pancreaticoduodenectomy (n = 1), distal pancreatectomy (n = 1) and total pancreatectomy (n = 1).

The final pathological diagnoses were: adenomas 5, borderline 1, noninvasive IPM carcinomas 2, minimally invasive IPM carcinoma 1, and non-IPMN invasive ductal carcinomas of pancreas 2. The lesions in all patients with a final diagnosis of malignant disease had shown progression with higher likelihood of malignancy on imaging, while the pathological diagnoses in the four patients who underwent surgery because of pancreatitis (n = 3) and synchronous carcinoid of papilla (n = 1) were adenomas in three cases and borderline IPMN in one case.

Incidence of pancreatic cancer

Pancreatic cancers developed in 6 of 103 patients (5.8%) during the follow-up. These included invasive ductal carcinoma of the pancreas (n = 2), noninvasive IPM carcinoma (n = 2), minimally