Combination chemotherapy regimens with platinum-based cisplatin plus an oral fluoropyrimidine are commonly used as first-line treatment for advanced gastric cancer in Japan [5]. This treatment regimen is based on early-phase clinical trials that showed cisplatin in combination with 5-fluorouracil (5-FU) or oral fluoropyrimidines yielded overall response rates of approximately 40% and median survival times of 7–13 months [6–10].

Vascular endothelial growth factor (VEGF) plays an essential role in the formation and maintenance of tumour vasculature [11]. The addition of bevacizumab, an anti-VEGF-A antibody, to standard chemotherapy has demonstrated clinical benefit in patients with advanced colorectal cancer [12–14] and non-small-cell lung cancer [15].

Cediranib is an oral, highly potent VEGF signalling inhibitor with activity against all three VEGF receptors [16, 17]. Initial clinical evaluation of cediranib monotherapy demonstrated that it is suitable for once-daily oral dosing in Japanese [18] and Western [19] patients, with biological activity at doses ≥20 mg/day [19]. Subsequent Phase I studies showed that cediranib 30 mg/day was generally well tolerated in combination with various standard anti-cancer treatments, with encouraging preliminary evidence of antitumour activity [20–23]. However, when the protocol for the present study was being developed, emerging data from Phase II and III trials indicated that cediranib 20 mg was the highest tolerable dose suitable for chronic once-daily dosing in combination with chemotherapy, with higher doses not considered to be more effective [24, 25]. Consequently, the dose of cediranib selected for this combination study was 20 mg/day. The primary objective of the current Phase I study (ClinicalTrials.gov, number NCT00960349) was to assess the safety and tolerability of cediranib 20 mg/day in combination with capecitabine/cisplatin or S-1/cisplatin in Japanese patients with previously untreated advanced gastric cancer.

Methods

Patients

Japanese patients ≥20 years of age with histologically or cytologically confirmed previously untreated recurrent or metastatic unresectable gastric adenocarcinoma were eligible for inclusion. Patients were required to have a life expectancy ≥12 weeks and a World Health Organization performance status of 0 or 1. The main exclusion criteria were as follows: significant respiratory, cardiac, hepatic or renal dysfunction; unstable brain metastases; poorly controlled hypertension; significant haemorrhage (>30 ml bleeding/episode in the previous 3 months) or haemoptysis (>5 ml fresh blood in the previous 4 weeks); arterial thromboembolic events in the previous 12 months; history of other malignancies within the previous 5 years; any unresolved toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) from prior radiotherapy; recent (<14 days) major thoracic or abdominal surgery; and incomplete recovery from prior surgery. All patients provided written informed consent. The study was approved by the institutional review board at each participating centre and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on Bioethics [26].

Study design

This was a multicentre, open-label, non-randomized, Phase I study. Eligible patients received cediranib 20 mg/day orally (starting on day 2 in cycle 1) in combination with either cisplatin (60 mg/m^2 intravenous [iv], day 1) plus S-1 (40–60 mg orally twice daily, days 1–21) [Arm A] or cisplatin (80 mg/m^2 iv, day 1) plus capecitabine (1,000 mg/m^2 orally twice daily, days 1–14) [Arm B] (Fig. 1). One cycle of treatment in Arm A was 5 weeks, and one cycle of treatment in Arm B was 3 weeks. The rest periods in Arms A (2 weeks) and B (1 week) were consistent with standard clinical practice for administration of S-1 and capecitabine, respectively. The chemotherapy treatments in Arms A and B were continued for a maximum of eight and six cycles, respectively. Thereafter, treatment of cediranib plus S-1/capecitabine could be continued until a discontinuation criterion was met. Patients were initially entered into Arm A. Following enrolment of six patients into Arm A, patients were then entered into Arm B.

The primary study objective was to assess the safety and tolerability of cediranib in combination with S-1/cisplatin or capecitabine/cisplatin. After entry of six evaluable patients in each arm, a safety review committee (SRC) discussed whether the regimen was tolerated. The treatment was considered tolerable if ≤1 of the six patients experienced a DLT. If 2–3 of the six patients experienced a DLT, either the SRC recommended the combination was tolerated or the cohort was expanded to include three further evaluable patients. If ≥4 patients experienced a DLT, the treatment was considered intolerable.

In both arms, a DLT was any toxicity considered related to study drug that commenced within the first 21 days of cycle 1 and met any of the following criteria: hypertension or diarrhoea that required cessation of cediranib treatment; an absolute neutrophil count <500/mm^3 for ≥5 days despite growth factor support; a platelet count <50,000/mm^3 for ≥5 days; a dose delay to starting any chemotherapy agent in cycle 2 for longer than 14 days; dose reductions of cediranib due to cediranib-related toxicity; a single increase from baseline in the QT interval corrected for heart rate

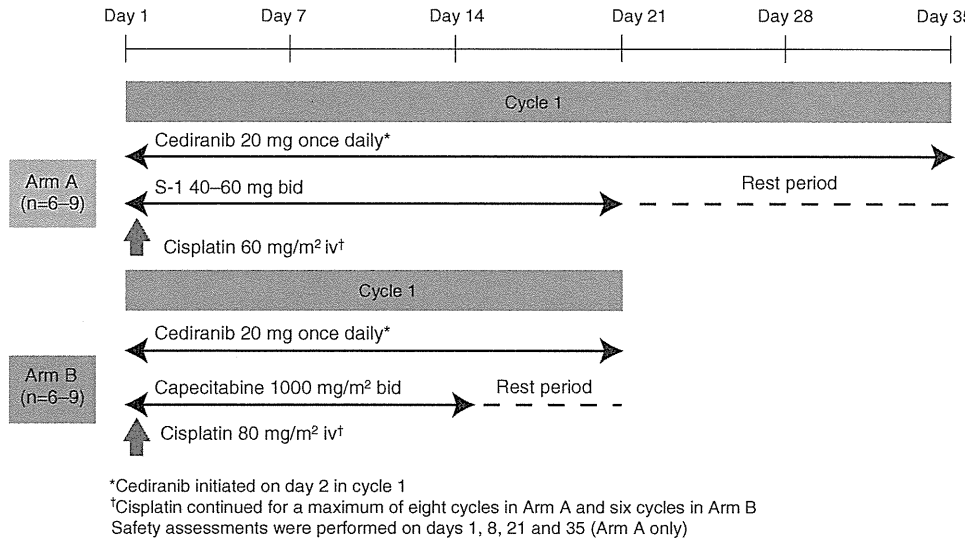

Fig. 1 Study design

*Cediranib initiated on day 2 in cycle 1
†Cisplatin continued for a maximum of eight cycles in Arm A and six cycles in Arm B
Safety assessments were performed on days 1, 8, 21 and 35 (Arm A only)

(QTc) of 60 ms that results in a QTc of at least 460 ms; two QTc measurements >490 ms taken at least 24 h apart; and any other CTCAE grade ≥3 that was, in the opinion of the investigator and the SRC, not clearly related to disease progression, clinically significant and related to the study drug.

Secondary objectives were to determine the steady-state pharmacokinetics (PK) of cediranib alone and in combination with chemotherapy and to investigate the potential effect of cediranib on the PK of the chemotherapy components (cisplatin and S-1/capecitabine [5-FU]). An exploratory objective was to assess the preliminary efficacy of the combination regimens by measurement of tumour response according to the Response Evaluation Criteria In Solid Tumours (RECIST version 1.0) [27].

Assessment of safety and tolerability

After a full physical examination at enrolment, toxicity was monitored throughout the study by the assessment of adverse events (AEs), which were graded according to CTCAE version 3.0. Vital signs (blood pressure [BP], pulse rate and body temperature) were measured, electrocardiograms recorded and samples taken for clinical chemistry, haematology assessment and urinalysis at the screening visit and on days 1, 8 and 21 in both arms; patients in Arm A repeated these assessments on day 35.

Pharmacokinetic assessment

To evaluate steady-state cediranib PK, blood samples were taken immediately before and 1, 2, 4, 6, 8 and 24 h after cediranib treatment on the final day of cycle 1 (cediranib alone) and day 1 of cycle 2 (presence of chemotherapy). To evaluate S-1/capecitabine (5-FU) PK, blood samples were collected immediately before and 0.5, 1, 2, 4, 6 and 8 h after S-1/capecitabine treatment on day 1 of cycle 1 (absence of cediranib) and day 1 of cycle 2 (presence of cediranib). To evaluate cisplatin PK, blood samples were taken pre-dose; 5 min before the end of the 2-h iv infusion; and 2.5, 3, 4, 6, 8 and 24 h post start of infusion on day 1 of cycle 1 (absence of cediranib) and day 1 of cycle 2 (presence of cediranib).

Plasma concentrations of cediranib, capecitabine (5-FU only), S-1 (5-FU only) and cisplatin (total platinum equivalents) were determined using high-performance liquid chromatography with mass spectrometry (LC–MS/MS). PK parameters were calculated using standard non-compartmental analysis.

Assessment of tumour response

Objective tumour assessments determined by RECIST were performed every 12 weeks from the start of treatment until disease progression, death or discontinuation of cediranib due to any other reason.

Results

Patient characteristics

Between August and December 2009, 14 patients were recruited into Arm A ($n = 6$) or Arm B ($n = 8$). Patient demographic and baseline characteristics are summarized in Table 1. At data cut-off (4 January 2010), three patients in Arm A and five patients in Arm B were still receiving cediranib, and one patient in Arm B continued to receive capecitabine and cisplatin. The reasons for discontinuation of cediranib treatment were clinical disease progression

Table 1 Patient demographics and baseline characteristics

Characteristics	Cediranib + S-1 + cisplatin ($n = 6$)	Cediranib + capecitabine + cisplatin ($n = 8$)	Total ($n = 14$)
Age, years			
Median	59.5	60.5	60.5
Range	53–71	27–72	27–72
Sex, *n* (%)			
Male	4 (66.7)	5 (62.5)	9 (64.3)
Female	2 (33.3)	3 (37.5)	5 (35.7)
WHO performance status, *n* (%)			
0	3 (50.0)	4 (50.0)	7 (50.0)
1	3 (50.0)	4 (50.0)	7 (50.0)
Number of metastatic sites (%)			
1	1 (16.7)	0	1 (7.1)
>1	5 (83.3)	8 (100.0)	13 (92.9)
Recurrence, *n* (%)	0	1 (12.5)	1 (7.1)
Stage IV, *n* (%)	6 (100)	7 (87.5)	13 (92.9)
Measurable target lesion, *n* (%)	5 (83.3)	6 (75.0)	11 (78.6)
Histology, *n* (%)			
Adenocarcinoma (intestinal)	1 (16.7)	3 (37.5)	4 (28.6)
Adenocarcinoma (diffuse)	1 (16.7)	0	1 (7.1)
Tubular adenocarcinoma	3 (50.0)	2 (25.0)	5 (35.7)
Signet ring carcinoma	1 (16.7)	3 (37.5)	4 (28.6)

WHO World Health Organization

(Arms A and B, $n = 1$), AEs (Arms A and B, $n = 1$) and withdrawal of consent (Arm A, $n = 1$). One patient in Arm B was revealed ineligible at cycle 2 due to a pulmonary embolism at baseline; this patient discontinued study treatment but was included in safety analyses.

Safety and tolerability

All patients received at least one dose of cediranib and were therefore evaluable for safety. The median (range) daily cediranib dose was 16.0 (12.9–20.0) mg in Arm A and 15.9 (13.7–20.0) mg in Arm B, and median (range) duration of actual exposure to cediranib was 72.5 days (13–127) for Arm A and 38.5 days (13–62) for Arm B. The median (range) number of chemotherapy cycles received was 2.5 (1–4) for both arms.

Overall, 12 (86%) [Arm A, $n = 5$; Arm B, $n = 7$] patients experienced one or more cediranib dose interruptions, with one patient from each arm having a dose reduction to 15 mg/day. All six patients in Arm A experienced a dose reduction or interruption of S-1 and seven patients (87.5%) in Arm B experienced a dose reduction or interruption of capecitabine. Five patients in each arm (Arm A, 83.3%; Arm B, 62.5%) had a dose reduction or dose delay of cisplatin. Two patients in Arm A (alopecia, $n = 1$; diarrhoea, stomatitis, fatigue, decreased appetite and hyponatraemia, $n = 1$) and one patient in Arm B (diarrhoea, fatigue, decreased appetite and hypomagnesaemia) experienced AEs that led to permanent discontinuation of cediranib treatment.

Table 2 Most common adverse events (incidence > 30% in total population)

AE, preferred term	All grades, *n* (%)		
	Cediranib + S-1 + cisplatin ($n = 6$)	Cediranib + capecitabine + cisplatin ($n = 8$)	Total ($n = 14$)
Decreased appetite	5	8	13 (92.9)
Fatigue	5	8	13 (92.9)
Nausea	5	8	13 (92.9)
Constipation	3	7	10 (71.4)
Diarrhoea	5	5	10 (71.4)
Stomatitis	4	6	10 (71.4)
Hypertension	3	6	9 (64.3)
Weight decreased	5	4	9 (64.3)
Neutropenia	5	3	8 (57.1)
Vomiting	3	5	8 (57.1)
Alopecia	2	4	6 (42.9)
Dysphonia	2	4	6 (42.9)
Hiccups	1	4	5 (35.7)
Leukopenia	3	2	5 (35.7)
Proteinuria	3	2	5 (35.7)

AE adverse event

DLTs were reported in one patient in Arm A (decreased appetite, grade 3) and one patient in Arm B (decreased appetite, fatigue and hyponatraemia; all grade 3). In Arm A, the investigator assessed that decreased appetite was related to S-1 and/or cisplatin. In Arm B, the investigator judged decreased appetite and hyponatraemia related to cediranib, S-1 and cisplatin, and stomatitis related to cediranib and S-1. The SRC decided neither DLT warranted cohort expansion for further evaluation of safety.

The most commonly reported AEs were decreased appetite, fatigue and nausea (all $n = 13$ [92.9%]) [Table 2]. Five (83%) patients in Arm A and six (75%) patients in Arm B experienced AEs grade ≥3 (Table 3). Hypertension was reported as an AE in nine patients (Arm A, $n = 3$; Arm B, $n = 6$), only one (Arm B) of which was

Table 3 Any CTCAE grade ≥3 adverse events

	Grade	Cediranib + S-1 + cisplatin ($n = 6$)	Cediranib + capecitabine + cisplatin ($n = 8$)	Total ($n = 14$)
Neutropenia	3	3	2	5 (35.7)
Hypokalaemia	3	0	3	3 (21.4)
Hyponatraemia	3	1	2	3 (21.4)
Decreased appetite	3	1	1	2 (14.3)
Fatigue	3	0	2	2 (14.3)
Anaemia	3	0	1	1 (7.1)
Diarrhoea	3	1	0	1 (7.1)
Haemoglobin decreased	3	1	0	1 (7.1)
Hyperbilirubinaemia	3	0	1	1 (7.1)
Hyperglycaemia	3	0	1	1 (7.1)
Hypertension	3	0	1	1 (7.1)
Hypomagnesaemia	3	0	1	1 (7.1)
Platelet count decreased	3	1	0	1 (7.1)
Pulmonary embolism	4	0	1	1 (7.1)
Stomatitis	3	1	0	1 (7.1)
Syncope	4	1	0	1 (7.1)
White blood cell count decreased	3	1	0	1 (7.1)
Wound infection	3	1	0	1 (7.1)

grade 3; no action was taken regarding dose adjustment. One patient in Arm A experienced grade 4 transient syncope on day 6, cycle 2. A head computed tomography (CT) scan showed no cerebral haemorrhage and the syncope resolved on the same day it appeared. The investigator considered this event to be related to cediranib, S-1 and cisplatin. One patient from Arm B experienced a grade 4 pulmonary embolism that was identified on day 18, cycle 2 after the patient complained of chest pain. After careful review of the baseline CT scan, the pulmonary embolism was found to be pre-existing at study entry. The investigator judged the event as worsening of the pulmonary embolism related to cediranib, capecitabine and cisplatin. Increases in thyroid stimulating hormone were observed in both arms, but free T4 and T3 remained within normal limits for the majority of these patients. Increases were observed in alanine aminotransferase and aspartate aminotransferase in both arms, but most values were generally within the normal ranges. There were no clinically relevant results related to electrocardiogram, physical findings or other safety observations.

Five serious AEs (SAEs) were reported in three patients in Arm A (decreased appetite, $n = 2$; hyponatraemia, $n = 1$; stomatitis, $n = 1$; syncope, $n = 1$), and in addition to the pulmonary embolism in one patient, three other SAEs were reported in a separate patient in Arm B (decreased appetite, hyponatraemia and fatigue). All SAEs, except for the pulmonary embolism, had resolved by data cut-off. There were no deaths in the period to data cut-off in either arm.

Pharmacokinetics

A summary of PK parameters for cediranib, cisplatin and S-1/capecitabine is shown in Table 4. Only six patients (Arm A, $n = 2$; Arm B, $n = 4$) were evaluable for PK analysis, having completed the planned sampling schedule; therefore, limited data were available for within-patient comparison. In Arm A ($n = 2$), the PK parameters for S-1 in combination with both cediranib and cisplatin were similar to those for S-1 when administered with cisplatin alone, and the PK parameters for cediranib were similar in the presence and absence of chemotherapy; however, there were insufficient data to draw meaningful conclusions on the PK in Arm A. Based on limited data from Arm B ($n = 4$), the cediranib PK parameters were similar in the absence and presence of capecitabine/cisplatin. The PK profile of capecitabine was generally similar in the absence and presence of cediranib; one patient (patient 4 in Table 4) had a higher exposure in the presence of cediranib, but the reason for this is not clear as no interaction would be expected. In all patients (Arms A and B), slight increases in exposure to cisplatin (total platinum equivalents; maximum plasma concentration [C_{max}] and area under plasma concentration–time curve from time zero to 8 h [AUC_{0-8h}]) were observed when cediranib was administered with chemotherapy compared with chemotherapy alone; however, samples collected in the absence of cediranib were obtained following single-dose cisplatin, whereas those collected in the presence of cediranib were obtained following multiple-dose cisplatin.

Efficacy

Seven patients (Arm A, $n = 4$; Arm B, $n = 3$) had a post-baseline scan and were therefore evaluable for efficacy. Tumour shrinkage was observed in five of these patients (Fig. 2); the mean largest change from baseline was −41.8% in Arm A ($n = 4$) and −26.3% in Arm B ($n = 3$). One patient in Arm A had a partial response that was ongoing at data cut-off (duration >79 days). Among the four patients with stable disease ($n = 2$ in each arm), three had unconfirmed partial responses at data cut-off. One patient in each arm had a best response of progressive disease.

Table 4 Summary of pharmacokinetic parameters

Analyte	Patient	Combination	C_{max}, ng/ml	AUC, ng h/ml
Arm A				
Cediranib	Patient 1	Cediranib alone	25.5	378
		Cediranib + S-1 + cisplatin	51.3	598
	Patient 2	Cediranib alone	153	2,640
		Cediranib + S-1 + cisplatin	192	2,780
5-FU	Patient 1 (60 mg S-1)	S-1 + cisplatin	58.6	302
		Cediranib + S-1 + cisplatin	92.1	446
	Patient 2 (50 mg S-1)	S-1 + cisplatin	182	908
		Cediranib + S-1 + cisplatin	130	644
Cisplatin	Patient 1	S-1 + cisplatin	2,740	12,700
		Cediranib + S-1 + cisplatin	3,040	14,100
	Patient 2	S-1 + cisplatin	2,400	10,400
		Cediranib + S-1 + cisplatin	2,790	12,600
Arm B				
Cediranib	All patients ($n = 4$)	Cediranib alone	77.5 (32.9–99.9)	1,180 (479–1,800)
	All patients ($n = 4$)	Cediranib + capecitabine + cisplatin	86.3 (50.2–115)	1,220 (687–1,850)
5-FU	Patient 3 (1,600 mg capecitabine)	Capecitabine + cisplatin	130	283
		Cediranib + capecitabine + cisplatin	284	421
	Patient 4 (1,750 mg capecitabine)	Capecitabine + cisplatin	132	187
		Cediranib + capecitabine + cisplatin	983	889
	Patient 5 (1,450 mg capecitabine)	Capecitabine + cisplatin	167	305
		Cediranib + capecitabine + cisplatin	105[a]	335[a]
	Patient 6 (1,600 mg capecitabine)	Capecitabine + cisplatin	287	518
		Cediranib + capecitabine + cisplatin	392[b]	647[b]
Cisplatin	All patients ($n = 4$)	Capecitabine + cisplatin	3,430 (2,720–3,840)	16,900 (13,500–18,900)
	All patients ($n = 4$)	Cediranib + capecitabine + cisplatin	4,620 (3,230–5,720)	21,700 (16,600–23,600)

AUC_{0-24h} was calculated for cediranib; AUC_{0-4h} for capecitabine (5-FU); and AUC_{0-8h} for cisplatin and S-1 (5-FU)

In Arm B, cediranib and cisplatin parameters are expressed as mean (min–max); all other data are individual patient values as there are insufficient data to summarize by mean value

AUC area under the plasma concentration–time curve, C_{max} maximum plasma (peak) drug concentration

[a] Dose of 1,300 mg capecitabine administered: data dose normalized to 1,450 mg

[b] Dose of 1,200 mg capecitabine administered: data dose normalized to 1,600 mg

Discussion

The impact of conventional chemotherapy on advanced gastric cancer remains modest, with median survival times reaching a plateau of 7–13 months [6–8]. More effective treatment options are needed. In this Phase I study, we evaluated the VEGF signalling inhibitor cediranib in combination with cisplatin and S-1 or capecitabine in Japanese patients with previously untreated locally advanced or metastatic unresectable gastric adenocarcinoma. Treatment was tolerable, with only one patient in each arm experiencing a DLT. Overall, the safety profile of each regimen was consistent with previous studies of the individual agents in patients with advanced cancer [8, 9, 18, 19, 23, 28–30], and no new toxicities were identified. The most commonly reported AEs were decreased appetite, fatigue and nausea. There were no reports of severe hypertension as a SAE, and the overall incidence of hypertension was consistent with that reported in a Phase I study of cediranib monotherapy in Japanese patients [18].

Insufficient PK data preclude any meaningful conclusions relating to Arm A. Based on the limited PK data from Arm B, there was no clear indication of a consistent interaction between cediranib and cisplatin/capecitabine. This is not unexpected as it is considered unlikely that cisplatin, capecitabine or S-1 would affect cediranib routes of metabolism [31]. The slight increases in cisplatin exposure observed in all patients when cediranib was administered with chemotherapy compared to chemotherapy alone may be due to an accumulation of platinum following multiple dosing.

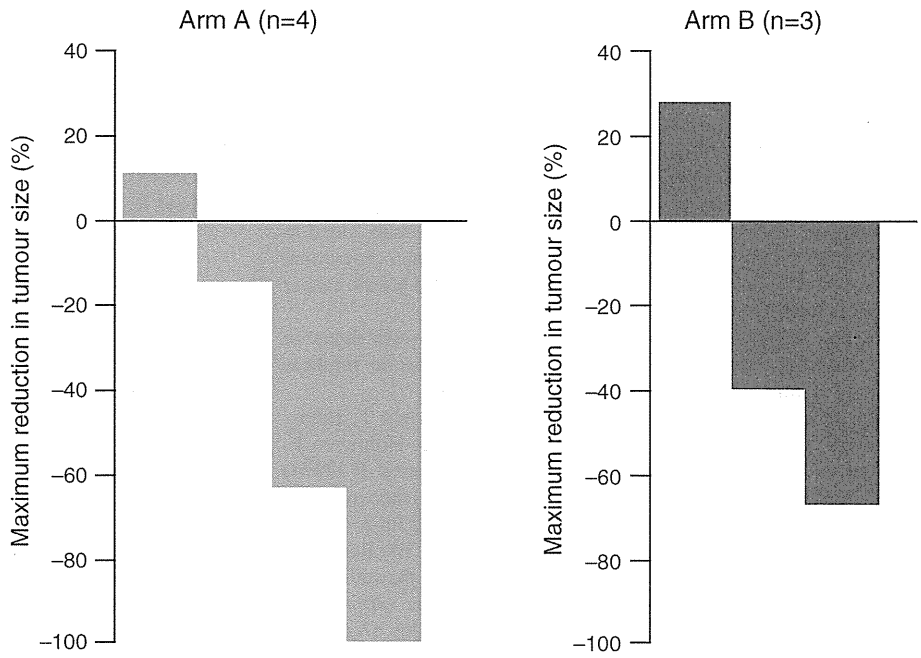

Fig. 2 Waterfall plot for best change in tumour size in each patient

In this small Phase I study, tumour shrinkage was observed in five of seven evaluable patients. This preliminary evidence of antitumour activity is consistent with the efficacy findings observed in an early-phase dose-finding study of sorafenib, a multi-targeted kinase inhibitor with activity versus VEGFR-2 and -3, in combination with capecitabine and cisplatin as a first-line treatment for patients with advanced gastric cancer [32]. However, targeting VEGF signalling with bevacizumab, an anti-VEGF-A monoclonal antibody, in patients with advanced gastric cancer met with disappointing results in the recently reported Phase III AVAGAST study [33]. This first-line study failed to meet its primary endpoint of improved overall survival with the addition of bevacizumab to cisplatin plus capecitabine/5-FU, although an efficacy analysis by geographical region revealed that, for both arms, median overall survival was greatest for patients who enrolled in the Asia/Pacific region. Despite the primary outcome of the AVAGAST study, the bevacizumab regimen showed significant advantages for the secondary efficacy endpoints of progression-free survival and overall response rate, suggesting that anti-VEGF treatment strategies are worthy of continued investigation in advanced gastric cancer.

In conclusion, cediranib 20 mg plus cisplatin and S-1 or capecitabine had a manageable tolerability profile as a first-line treatment in Japanese patients with advanced gastric cancer and showed preliminary evidence of antitumour activity.

Acknowledgments Funding for this study was provided by AstraZeneca. We thank Paul Williams, PhD, from Mudskipper Bioscience, who provided medical writing assistance funded by AstraZeneca.

Conflict of interest X.S. and K.H.B. are employees of AstraZeneca and own stock. T.S., Y.Y, K.M., H.H., Y.S., D.T., K.T., T.E.N. and N.B. declare no conflicts of interest.

References

1. GLOBOCAN statistics. 2008. Available at http://globocan.iarc.fr/
2. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M (1993) Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 72:37–41
3. Glimelius B, Hoffman K, Haglund U, Nyren O, Sjoden PO (1994) Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol 5:189–190
4. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M (1995) 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 71: 587–591
5. Fujii M, Kochi M, Takayama T (2010) Recent advances in chemotherapy for advanced gastric cancer in Japan. Surg Today 40:295–300
6. Ohtsu A, Shimada Y, Yoshida S, Saito H, Seki S, Morise K, Kurihara M (1994) Phase II study of protracted infusional 5-fluorouracil combined with cisplatinum for advanced gastric cancer: report from the Japan clinical oncology group (JCOG). Eur J Cancer 30A:2091–2093
7. Koizumi W, Kurihara M, Sasai T, Yoshida S, Morise K, Imamura A, Akazawa S, Betsuyaku T, Ohkubo S, Takahashi H et al (1993) A phase II study of combination therapy with 5′-deoxy-5-fluorouridine and cisplatin in the treatment of advanced gastric cancer with primary foci. Cancer 72:658–662
8. Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, Shirao K, Matsumura Y, Gotoh M (2003) Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 89:2207–2212

9. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
10. Van Cutsem E, Kang Y, Chung H, Shen L, Sawaki A, Lordick F, Hill J, Lehle M, Feyereislova A, Bang Y (2009) Efficacy results from the ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). J Clin Oncol 27(18S):abst LBA4509
11. Ferrara N (2002) Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: therapeutic implications. Semin Oncol 29:10–14
12. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335–2342
13. Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S (2005) Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol 23: 3706–3712
14. 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
15. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542–2550
16. Heckman CA, Holopainen T, Wirzenius M, Keskitalo S, Jeltsch M, Wedge SR, Jürgensmeier JM (2007) Inhibition of VEGF-C-induced VEGFR-3 activity and lymphatic endothelial cell function by the tyrosine kinase inhibitor AZD2171. Proc Am Assoc Cancer Res 48:abst 2999
17. Wedge SR, Kendrew J, Hennequin LF, Valentine PJ, Barry ST, Brave SR, Smith NR, James NH, Dukes M, Curwen JO, Chester R, Jackson JA, Boffey SJ, Kilburn LL, Barnett S, Richmond GH, Wadsworth PF, Walker M, Bigley AL, Taylor ST, Cooper L, Beck S, Jürgensmeier JM, Ogilvie DJ (2005) AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res 65:4389–4400
18. Yamamoto N, Tamura T, Yamamoto N, Yamada K, Yamada Y, Nokihara H, Fujiwara Y, Takahashi T, Murakami H, Boku N, Yamazaki K, Puchalski TA, Shin E (2009) Phase I, dose escalation and pharmacokinetic study of cediranib (RECENTIN), a highly potent and selective VEGFR signaling inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 64:1165–1172
19. Drevs J, Siegert P, Medinger M, Mross K, Strecker R, Zirrgiebel U, Harder J, Blum H, Robertson J, Jürgensmeier JM, Puchalski TA, Young H, Saunders O, Unger C (2007) Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol 25:3045–3054
20. Laurie SA, Gauthier I, Arnold A, Shepherd FA, Ellis PM, Chen E, Goss G, Powers J, Walsh W, Tu D, Robertson J, Puchalski TA, Seymour L (2008) Phase I and pharmacokinetic study of daily oral AZD2171, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with carboplatin and paclitaxel in patients with advanced non-small-cell lung cancer: the National Cancer Institute of Canada clinical trials group. J Clin Oncol 26:1871–1878
21. Chen E, Jonker D, Gauthier I, Maclean M, Wells J, Powers J, Seymour L (2009) Phase I study of cediranib in combination with oxaliplatin and infusional 5-fluorouracil in patients with advanced colorectal cancer. Clin Cancer Res 15:1481–1486
22. Goss G, Shepherd FA, Laurie S, Gauthier I, Leighl N, Chen E, Feld R, Powers J, Seymour L (2009) A phase I and pharmacokinetic study of daily oral cediranib, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer: a study of the National Cancer Institute of Canada Clinical Trials Group. Eur J Cancer 45:782–788
23. LoRusso P, Shields AF, Gadgeel S, Vaishampayan U, Guthrie, T, Puchalski T, Xu J, Liu Q (2010) Cediranib in combination with various anticancer regimens: results of a phase I multi-cohort study. Invest New Drugs. doi:10.1007/s10637-010-9484-5. Epub ahead of print
24. Goss GD, Arnold A, Shepherd FA, Dediu M, Ciuleanu TE, Fenton D, Zukin M, Walde D, Laberge F, Vincent MD, Ellis PM, Laurie SA, Ding K, Frymire E, Gauthier I, Leighl NB, Ho C, Noble J, Lee CW, Seymour L (2010) Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small-cell lung cancer: NCIC clinical trials group BR24 study. J Clin Oncol 28:49–55
25. Robertson JD, Botwood NA, Rothenberg ML, Schmoll H-J (2009) Phase III trial of FOLFOX plus bevacizumab or cediranib (AZD2171) as first-line treatment of patients with metastatic colorectal cancer: HORIZON III. Clin Colorectal Cancer 8:59–60
26. AstraZeneca (2011) Global policy: bioethics. Available at http://www.astrazeneca.com/Responsibility/Code-policies-standards/Policiesstandards
27. Therasse P (2002) Measuring the clinical response. What does it mean? Eur J Cancer 38:1817–1823
28. vanCruijsen H, Voest EE, van Herpen CML, Hoekman K, Witteveen PO, Tjin-A-Ton ML, Punt CJ, Puchalski T, Milenkova T, Giaccone G (2006) Phase I evaluation of AZD2171, a highly potent, selective VEGFR signaling inhibitor, in combination with gefitinib, in patients with advanced tumors. J Clin Oncol 24(S18):abst 3017
29. Lee SS, Lee JL, Ryu MH, Chang HM, Kim TW, Kang HJ, Kim WK, Lee JS, Kang YK (2007) Combination chemotherapy with capecitabine (X) and Cisplatin (P) as first line treatment in advanced gastric cancer: experience of 223 patients with prognostic factor analysis. Jpn J Clin Oncol 37:30–37
30. Lee JO, Lee KW, Oh DY, Kim JH, Im SA, Kim TY, Bang YJ (2009) Combination chemotherapy with capecitabine and cisplatin for patients with metastatic hepatocellular carcinoma. Ann Oncol 20:1402–1407
31. Schulz-Utermoehl T, Spear M, Pollard CR, Pattison C, Rollison H, Sarda S, Ward M, Bushby N, Jordan A, Harrison M (2010) In vitro hepatic metabolism of cediranib, a potent vascular endothelial growth factor tyrosine kinase inhibitor: interspecies comparison and human enzymology. Drug Metab Dispos 38:1688–1697
32. Kim C, Lee J-L, Choi YH, Kang BW, Ryu M-H, Chang HM, Kim TW, Kang Y-K (2011) Phase I dose-finding study of sorafenib in combination with capecitabine and cisplatin as a first-line treatment in patients with advanced gastric cancer. Invest New Drugs. doi:10.1007/s10637-010-9531-2. Epub ahead of print
33. Kang Y, Ohtsu A, Van Cutsem E, Rha SY, Sawaki A, Park P, Lim H, Wu J, Langer B, Shah MA (2010) AVAGAST: a randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC). J Clin Oncol 28(18S):abst LBA4007

Int J Clin Oncol
DOI 10.1007/s10147-011-0335-y

ORIGINAL ARTICLE

Comparison of safety and efficacy of S-1 monotherapy and S-1 plus cisplatin therapy in elderly patients with advanced gastric cancer

Takahiro Tsushima · Shuichi Hironaka · Narikazu Boku · Nozomu Machida · Kentaro Yamazaki · Hirofumi Yasui · Akira Fukutomi · Akiko Todaka · Hiroya Taniguchi · Yusuke Onozawa · Keisei Taku

Received: 15 July 2011 / Accepted: 23 September 2011

Abstract
Background Although S-1 plus cisplatin (SP) therapy is recognized as the standard treatment for advanced gastric cancer (AGC) in Japan, its safety and efficacy in elderly patients have not been investigated sufficiently.
Methods We retrospectively reviewed the data of 58 patients with AGC selected from 82 consecutive patients who were ≥70 years old and were treated with SP or S-1 monotherapy as the first-line therapy. In SP, S-1 (40 mg/m^2, bid) was administered for 3 weeks and cisplatin (60 mg/m^2) on day 8, every 5 weeks. In S-1 monotherapy, S-1 (40 mg/m^2, bid) was administered for 4 weeks, every 6 weeks.
Results SP and S-1 was administered in 21 and 37 patients, respectively. There were some differences in patient characteristics between the treatment groups, such as histological type ($P = 0.16$); the presence of liver metastasis ($P = 0.07$); and the presence of peritoneal metastasis ($P = 0.02$). The incidences of grade 3/4 hematological toxicities were 57% (12/21) in the SP and 35% (13/37) in the S-1 group ($P = 0.17$). Those of non-hematological toxicities were 14% (3/21) and 14% (5/37) for anorexia, 10% (2/21) and 14% (5/37) for fatigue, and 5% (1/21) and 5% (2/37) for nausea in the SP and S-1 groups, respectively. Median progression-free survival and median overall survival in the SP and S-1 groups were 5.0 and 5.2 months, and 14.4 and 10.9 months, respectively.
Conclusion SP and S-1 therapy were both feasible in elderly patients, though there is the risk of a high incidence of hematological toxicities.

Keywords S-1 · Cisplatin · Elderly · Feasibility · Efficacy

T. Tsushima (✉) · S. Hironaka · N. Boku · N. Machida · K. Yamazaki · H. Yasui · A. Fukutomi · A. Todaka · H. Taniguchi · Y. Onozawa · K. Taku
Division of Gastrointestinal Oncology,
Shizuoka Cancer Center, 1007 Shimonagakubo,
Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: t.tsushima@scchr.jp

S. Hironaka
Clinical Trial Promotion Department,
Chiba Cancer Center, Chiba, Japan

N. Boku
Department of Clinical Oncology, St. Marianna University
School of Medicine, Kanagawa, Japan

Y. Onozawa
Division of Medical Oncology,
Shizuoka Cancer Center, Shizuoka, Japan

K. Taku
Division of Medical Oncology,
Shizuoka General Hospital, Shizuoka, Japan

Introduction

With more than 800,000 new cases per year reported globally, gastric cancer is the second most common cause of cancer death [1, 2]. Systemic chemotherapy prolongs survival and improves quality of life in patients with advanced gastric cancer (AGC), compared to the best supportive care provided alone [3–5]. In Japan, the combination chemotherapy of S-1 plus cisplatin (SP) is recognized as a standard treatment for AGC from the results of pivotal phase III studies [6–8].

The population of elderly patients is increasing rapidly all over the world, and age is the most significant risk factor for the survival of various kinds of cancer patients [9]. However, it is uncertain whether evidence on the safety and efficacy of treatments from clinical trials is also

Published online: 22 October 2011

applicable to patients who are 70 years or older, because the proportion of elderly patients included in most clinical trials is small: patients over 70 years old accounted for less than 25% in the Japan Clinical Oncology Group (JCOG) 9912 trial [6] and only 17% in the S-1 plus cisplatin versus S-1 alone for first-line treatment of AGC (SPIRITS) trial, which compared SP therapy to S-1 monotherapy alone [7]. The subset analysis of the SPIRITS trial showed that the hazard ratio for overall survival in elderly patients between 70 and 74 years old was 0.95, while that in the whole study population was 0.77. Therefore, a different treatment strategy might be necessary for elderly cancer patients.

In the present single-institution retrospective study, we assessed the safety and efficacy of SP therapy and S-1 monotherapy in elderly patients with AGC.

Materials and methods

Patients

The subjects of this study were patients with unresectable or recurrent gastric cancer who received SP therapy or S-1 monotherapy at the Shizuoka Cancer Center between September 2002 and March 2008. The patient selection criteria were as follows: age 70 years or older; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; histologically proven adenocarcinoma; absence of history of prior chemotherapy; adequate oral intake; adequate bone marrow, renal, and hepatic functions (absolute neutrophil count of 1,500/μl or more, platelet count 10,000/μl or more, serum creatinine of 1.5 mg/dl or less, serum transaminase levels less than 100 IU/l or less than 200 IU/l if hepatic metastasis existed); presence of at least one non-curative factor other than positive peritoneal washing cytology; and absence of concomitant malignancy. A measurable lesion was not mandatory.

Treatment dose and schedule

In SP therapy, S-1 was administered orally at a dose of 40 mg/m^2 bid on day 1 through day 21 followed by 14 days of rest, with cisplatin 60 mg/m^2 being administered intravenously on day 8. This regimen was repeated every 35 days until detection of disease progression, appearance of unacceptable toxicities, or the patient's refusal to continue treatment. In S-1 monotherapy, S-1 40 mg/m^2 bid was administered on day 1 through day 28, followed by 14 days of rest, until any of the above-mentioned events occurred. In each treatment group, the dose of S-1 was determined according to the body surface area (BSA), as follows: 40 mg bid for BSA less than 1.25 m^2; 50 mg bid for BSA 1.25–1.5 m^2; 60 mg bid for BSA over 1.5 m^2.

These treatments were administered according to standard clinical practice. All physicians generally adhered to the following treatment modification criteria. If a grade 3 or higher adverse event, grade 2 increase of creatinine, or grade 2 infection occurred, treatment was suspended during the cycle or the start of the subsequent cycle was delayed until recovery of non-hematological toxicities grade 1 or lower, the neutrophil count reached more than 1,500/μl, and the platelet count reached more than 7.5 $\times$ 10^4/l. The dose of S-1 and cisplatin was reduced if any of the following adverse drug reactions occurred during the previous cycle: grade 4 leukocytopenia, anemia, or thrombocytopenia; or grade 3 or higher non-hematological toxicities.

Efficacy and toxicity evaluation

We retrospectively obtained all the clinical data from the medical records. Physical examinations and laboratory tests were repeated at least once every 3 weeks. Data on adverse events were collected until 30 days from the last administration or initiation of the subsequent chemotherapy, whichever occurred earlier. We evaluated adverse events on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Response evaluation was repeated at least once every 2 months. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Statistical analysis

Differences in the distribution of variables were evaluated using the Fisher exact test or Mann–Whitney *U* test, as appropriate. Patients who did not have a target lesion were excluded from the response 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 to the last date of confirmation that the patient was alive in the census. Progression-free survival (PFS) was defined as the period from the date of the first administration of S-1 to the earliest date of detection of tumor progression by imaging, or symptomatic deterioration clinically judged to be caused by disease progression, or the last date that the patient was confirmed to be alive without disease progression in the census. Survival curves were drawn by the Kaplan–Meier method.

The following variables were examined in the univariate analysis of OS and PFS: treatment, age, sex, PS, presence of complications, prior gastrectomy, creatinine clearance, histological type, presence of target lesions, number of metastatic sites, presence of liver metastasis, peritoneal metastasis, and lymph node metastasis. Multivariate analysis included potentially predictive variables for the risk of

disease progression or death in univariate analysis. $P < 0.05$ was considered significant.

All statistical analyses were performed using Dr. SPSS II (SPSS Japan Inc., Japan). Written informed consent was obtained from all the patients before starting the chemotherapy.

Results

Patient characteristics

A total of 82 consecutive patients with gastric cancer who were 70 years or older received SP therapy or S-1 monotherapy between September 2002 and March 2008 at the Shizuoka Cancer Center. Among them, 24 patients were excluded for the following reasons: absence of non-curative factor other than positive peritoneal washing cytology (10 patients), organ dysfunction (7 patients), absence of histological confirmation of adenocarcinoma (6 patients), and concomitant malignancy (1 patient). Therefore, 58 patients were included as subjects in this study; of them, 21 patients were treated with SP therapy and 37 were treated with S-1 monotherapy.

Patient characteristics are shown in Table 1. There were some differences in background between subjects in the SP and S-1 groups, such as histologically determined intestinal type (48 vs. 62%, respectively; $P = 0.16$); the presence of liver metastasis (57 vs. 32%, respectively; $P = 0.07$); and the presence of peritoneal metastasis (14 vs. 43%, respectively; $P = 0.02$).

Table 1 Patient backgrounds

	SP group	S-1 group	*P* value
Number of patients	21	37	
Age (years), median (range)	73 (70–82)	73 (70–80)	0.51
Age ≤75	17 (81%)	25 (68%)	0.27
Age >75	4 (19%)	12 (32%)	
Sex			0.97
Male	16 (76%)	28 (76%)	
Female	5 (24%)	9 (24%)	
ECOG performance status			0.78
0	7 (33%)	14 (38%)	
1	13 (62%)	21 (57%)	
2	1 (5%)	2 (5%)	
Complications			0.28
+	10 (48%)	23 (62%)	
−	11 (52%)	14 (38%)	
Prior gastrectomy			0.82
+	9 (43%)	17 (46%)	
−	12 (57%)	20 (54%)	
Creatinine clearance			0.60
Median (range) (ml/min)	63.2 (40–125.8)	63.9 (35.9–98.7)	
Histological type			0.16
Intestinal	10 (48%)	23 (62%)	
Diffuse	11 (52%)	14 (38%)	
Tumor status			0.22
Metastatic	14 (67%)	30 (81%)	
Recurrent	7 (33%)	7 (19%)	
Metastatic sites			
Liver	12 (57%)	12 (32%)	0.07
Peritoneum	3 (14%)	16 (43%)	0.02
Lymph node	14 (66%)	21 (57%)	0.46
Target lesions			0.65
+	18 (86%)	30 (81%)	
−	3 (14%)	7 (19%)	
Number of metastatic sites			0.64
0	1 (5%)	0 (0%)	
1	7 (33%)	13 (35%)	
2	11 (52%)	19 (51%)	
≥3	2 (10%)	5 (14%)	

Exposure to treatment

The median number of treatment cycles for SP was 3 (range 1–8) and for S-1 was 4 (range 1–18). Treatment modification was required in 11 SP patients (52%) and in 21 S-1 patients (57%) as follows: dose reduction in 3 patients (14%) and in 14 patients (38%), and delay of the subsequent cycle in 9 patients (43%) and in 14 patients (38%), respectively. Both dose reduction and subsequent cycle delay were required in 1 SP patient and in 7 S-1 patients. The median relative dose intensity per patient of S-1 and cisplatin was 80% (range 42–96%) and 82% (range 55–100%), respectively, in the SP group, and that of S-1 was 86% (range 54–100%) in the S-1 group. The main reason for treatment failure was disease progression in both treatment arms: 76% in SP and 92% in S-1 groups. In addition, 19% of patients in the SP group stopped treatment because of adverse events.

Adverse events

The adverse events are shown in Table 2. The incidences of grade 3 or higher hematological toxicities were greater in the SP group (12/21: 57%) than in the S-1 group (13/37: 35%), although the difference was not statistically significant ($P = 0.10$). Incidences of specific hematological toxicities for the SP and S-1 groups were 33% (7/21) and 5% (2/37) for neutropenia, 43% (9/21) and 32% (12/37) for anemia, and 19% (4/21) and 0% (0/37) for thrombocytopenia, respectively. The incidence of grade 3 or higher

non-hematological toxicities was similar in both treatment groups: 14% (3/21) and 14% (5/37) for anorexia, 10% (2/21) and 14% (5/37) for fatigue, and 5% (1/21) and 5% (2/37) for nausea in the SP and S-1 groups, respectively. The median creatinine clearance calculated by the Cockcroft–Gault equation was 53.4 and 56.0 ml/min, respectively, in the 10 patients of SP and 14 of S-1 who experienced grade 3 or 4 toxicity (excluding that of anemia). The median creatinine clearance was 64.1 and 66.8 ml/min in patients who did not experience grade 3 or 4 toxicity in the SP and S-1 groups, respectively.

One patient from each treatment group died within 30 days of the last administration of chemotherapy. One was a 74-year-old man from the SP group, who started S-1 at the standard dose after palliative total gastrectomy. After administration of cisplatin on day 8, he received hydration therapy from day 11 to 14 for the treatment of anorexia (grade 2) and diarrhea (grade 1). After recovering from these symptoms, he was discharged from the hospital on day 15. On day 18, he suffered from diarrhea again, and was admitted to another hospital. Despite intensive care, he died on day 27 because of arrythmia. In this case, the possibility of treatment-related death could not be excluded, because dehydration due to severe diarrhea might have caused the arrythmia. The other patient from the S-1 group was a 74-year-old man who presented after gastrojejunostomy for obstruction due to the primary tumor. He received the standard dose of S-1, and visited our hospital on days 15 and 29 in the first cycle without any serious adverse events. However, he was found dead at home on day 38. He had no specific concomitant disease except mild hypertension. The cause of death was diagnosed as acute heart failure, and it is possible that S-1 contributed to his death.

Table 3 Response in patients with target lesions

	SP group ($n = 18$)	S-1 group ($n = 30$)
Best overall response		
CR	1	2
PR	8	12
SD	3	8
PD	6	7
NE	0	1
Response proportion (%)	50.0	46.7

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluated

Response and survival

Eighteen patients in the SP group and 30 in the S-1 group had measurable lesions. The objective response rate was 9/18 (50.0%) in the SP group and 14/30 (46.7%) in the S-1 group. Among the responders, complete response was obtained in one patient in the SP group and 2 in the S-1 group (Table 3).

Twenty-one patients in the SP group and 37 in the S-1 group were involved in the PFS and OS analysis. The curves of PFS and OS for the SP and S-1 groups almost overlapped (Figs. 1, 2). The median PFS was 5.0 months in the SP group and 5.2 months in the S-1 group [hazard ratio (HR): 1.18, 95% confidence interval (CI): 0.68–2.06]. The median survival time (MST) was 14.4 months in the SP group and 10.9 months in S-1 (HR: 0.99, 95% CI: 0.57–1.71). The proportion of patients who received subsequent chemotherapy was similar in the SP and S-1 groups: 62% (13/21) and 65% (24/37), respectively.

Table 2 Adverse events

	SP group ($n = 21$)				S-1 group ($n = 37$)			
	G1/2	G3	G4	≥G3 (%)	G1/2	G3	G4	≥G3 (%)
Hematological								
Leukocytopenia	8	5	1	29	16	1	0	3
Neutropenia	7	5	2	33	8	2	0	5
Anemia	12	5	4	43	24	12	0	32
Thrombocytopenia	12	3	1	19	8	0	0	0
Non-hematological								
Febrile neutropenia	–	0	0	0	–	0	0	0
Fatigue	10	1	1	10	16	5	0	14
Anorexia	16	2	1	14	18	5	0	14
Diarrhea	5	1	0	5	12	0	0	0
Stomatitis	4	0	0	0	13	1	0	3
Nausea	11	1	0	5	9	2	0	5
Vomiting	2	0	0	0	6	0	0	0

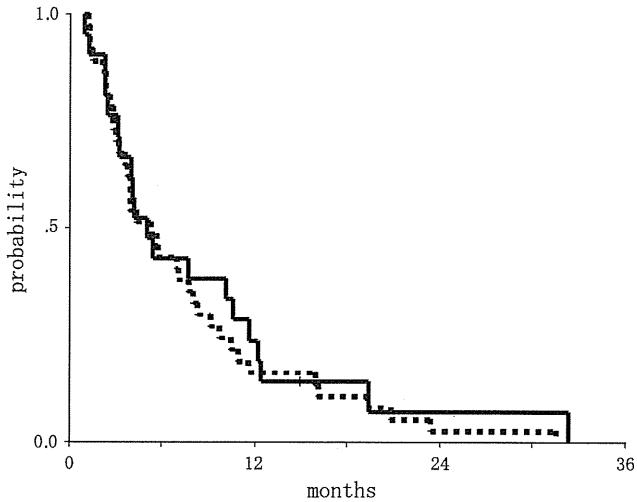

Fig. 1 Progression-free survival (PFS). The median PFS was 5.0 months in the SP group ($n = 21$, *solid line*) and 5.2 months in the S-1 group ($n = 37$, *dotted line*). The hazard ratio was 1.18, and the 95% confidence interval was 0.68–2.06

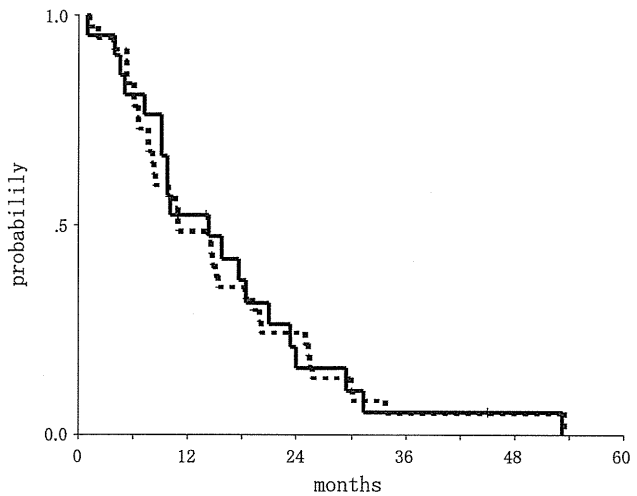

Fig. 2 Overall survival (OS). The median survival time was 14.4 months in the SP group ($n = 21$, *solid line*), and 10.9 months in the S-1 group ($n = 37$, *dotted line*). The hazard ratio was 0.99, and the 95% confidence interval was 0.57–1.71

Multivariate analysis showed that poor PS was the only factor associated with shorter OS (HR: 2.12, 95% CI: 1.37–3.26, $P = 0.001$) among the three potentially predictive variables selected by univariate analysis (age, PS, presence of peritoneal metastasis), while there was no predictive variable for PFS.

Discussion

Following the results of pivotal phase III trials, SP therapy is considered the standard chemotherapy in patients with unresectable or recurrent gastric cancer in Japan [6–8]. In the SPIRITS trial, the survival benefit of SP therapy over S-1 monotherapy was demonstrated with acceptable toxicity levels; however, the subset analysis showed that the hazard ratio in patients who were 70 years or older was 0.95 (95% CI: 0.71–1.27) [7]. However, because the subset analysis contained only 50 patients (17%) who were 70 years or older, there is uncertainty about the superiority of SP therapy over S-1 monotherapy in elderly patients with AGC. Thus, further investigation of SP therapy and S-1 monotherapy in elderly gastric cancer patients is necessary.

Because this study was retrospective, patient backgrounds between the two groups were not well balanced. In the S-1 group, the proportion of patients with peritoneal metastasis was significantly higher than in the SP group. Peritoneal metastasis is generally considered to be one of the unfavorable factors relating to shorter survival time in AGC; the patients included in the prognostic model had radiologically evident peritoneal metastasis or massive ascites [10]. In contrast, in the subset analysis of the JCOG 9912 trial, excluding the patients with severe peritoneal metastasis, patients without measurable lesions, mainly those with mild peritoneal metastasis, survived longer than those with measurable lesions [6]. Furthermore, in a randomized phase II study comparing S-1 and capecitabine, for which eligibility criteria included adequate oral intake, peritoneal metastasis was not a prognostic factor for OS [11]. Therefore, controversy exists over whether or not peritoneal metastasis is a prognostic factor in AGC. In our study, peritoneal metastasis was diagnosed in 10 out of 16 patients in the S-1 group and in 1 out of 3 patients in the SP group by laparotomy, not by radiological assessment. Because all patients had adequate oral intake, the peritoneal metastasis of most patients in this study was not so severe (only one patient had massive ascites), and therefore we consider that the presence or absence of peritoneal metastasis may not have had a major impact on survival. In the present study, the response rates in the SP and S-1 groups were 50.0 and 46.7%, respectively, and MST was 14.4 and 10.9 months, respectively. Though MST seemed longer in the SP group, the Kaplan–Meier curves of both treatment groups almost overlapped, and the hazard ratio was 0.98 (95% CI: 0.57–1.69). This hazard ratio of SP therapy over S-1 monotherapy was very similar to that of the subset analysis of elderly patients in the SPIRITS trial [7].

The relative dose intensity in the SP and S-1 groups was over 80% for each drug. Dose reduction was required in 14% of SP group subjects and 38% of S-1 group subjects. Though there was a higher incidence of grade 3 or 4 hematological toxicities in the SP group than the S-1 group, only one patient of SP needed dose reduction because of hematological toxicity. Most dose modifications were required because of non-hematological toxicities, the incidences of which were similar between the SP group and

Table 4 The incidence of grade 3 or 4 adverse events (%)

	Present study		SPIRITS trial	
	SP group ($n = 21$)	S-1 group ($n = 37$)	SP group ($n = 148$)	S-1 group ($n = 150$)
Hematological				
Leukocytopenia	28.6	2.7	11	2
Neutropenia	33.3	5.4	40	11
Anemia	42.9	32.4	26	4
Thrombocytopenia	19.0	0	5	0
Non-hematological				
Febrile neutropenia	0	0	3	1
Fatigue	9.5	13.5	4	1
Anorexia	14.3	13.5	30	6
Diarrhea	4.8	0	4	3
Stomatitis	0	2.7	0.7	0
Nausea	4.8	5.4	11	1
Vomiting	0	0	4	2

the S-1 group. Chemotherapy in both treatment groups was discontinued due to disease progression in many patients. It was evident that both treatments were feasible even in elderly patients.

The incidence of grade 3 or higher adverse events in the present study was more frequent than in the SPIRITS trial (Table 4), which could possibly be attributed to decreased creatinine clearance. In this study, patients with poor renal function experienced more severe adverse events. The pharmacokinetics of S-1 are dependent on renal function because 5-chloro-2,4-dihydroxypyridine, which is an inhibitor of dihydropyrimidine dehydrogenase [12–17], is eliminated through the kidneys. Organ functions, including renal function in the elderly, are likely to be somewhat impaired, and it has been reported that the glomerular filtration rate generally decreases with age [18]. The decreased creatinine clearance might lead to more frequent and severe toxicities associated with S-1, especially in elderly patients. Therefore, it is necessary to consider renal function before starting S-1-based chemotherapy, especially in elderly patients.

In geriatric oncology, neither the Karnofsky Performance Scale Index nor ECOG PS may be reliable for assessing physical status because comorbidities in elderly patients might affect their physical or mental status [19]. It has been reported that assessment of the condition of elderly cancer patients measured by comprehensive geriatric assessment (CGA) is useful for predicting tolerance to chemotherapy and survival [20–22]. CGA is a multidimensional evaluation scale of an elderly patient's physical performance, comorbidity, cognition, psychological stage, socioeconomic status, nutritional status, and medications [23, 24]. In some clinical trials targeting elderly cancer patients, functional assessment scales were adopted for patient selection in addition to PS and organ function assessments [25, 26]. In this study, PS was the only factor associated with survival. In addition, CGA might interfere with measurement of PS, as demonstrated in previous studies [20, 24, 27]. Thus it is suggested that CGA might also affect the clinical outcomes, especially the survival rates, of gastric cancer patients treated with chemotherapy.

In conclusion, SP therapy and S-1 monotherapy were both feasible in elderly patients with AGC, though the superiority of SP therapy over S-1 monotherapy was not so prominent in this review. Further clinical trials are warranted to establish a new standard care, especially in elderly gastric cancer patients.

Conflict of interest No author has any conflict of interest.

References

1. Munoz N, Franceschi S (1997) Epidemiology of gastric cancer and perspectives for prevention. Salud Publica Mex 39:318–330
2. Kamangar F, Dores GM, Anderson WF (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24:2137–2150
3. Murad AM, Santiago FF, Petroianu A et al (1993) Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 72:37–41
4. Glimelius B, Hoffman K, Haglund U et al (1994) Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol 5:189–190
5. Pyrhonen S, Kuitunen T, Nyandoto P et al (1995) Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus best supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 71:587–591
6. Boku N, Yamamoto S, Fukuda H et al (2009) Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10:1063–1069
7. Koizumi W, Narahara H, Hara T et al (2007) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
8. Narahara H, Iishi H, Imamura H et al (2011) 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 14:72–80
9. Jemal A, Siegel R, Ward E et al (2009) Cancer statistics, 2009. CA Cancer J Clin 59:225–249
10. Koo DH, Ryoo BY, Kim HJ et al (2011) A prognostic model in patients who receive chemotherapy for metastatic or recurrent gastric cancer: validation and comparison with previous models. Cancer Chemother Pharmacol 68:913–921
11. Lee JL, Kang YK, Kang HJ et al (2008) A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 99:584–590
12. Lichtman SM, Wildiers H, Chatelut E et al (2007) International society of geriatric oncology chemotherapy taskforce: evaluation

of chemotherapy in older patients—an analysis of the medical literature. J Clin Oncol 25:1832–1843
13. Lichtman SM, Boparai MK (2008) Anticancer drug therapy in the older cancer patient: pharmacology and polypharmacy. Curr Treat Options Oncol 9:191–203
14. Hurria A, Lichtman SM (2008) Clinical pharmacology of cancer therapies in older adults. Br J Cancer 98:517–522
15. Tatsumi K, Fukushima M, Shirasaka T et al (1987) Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. Jpn J Cancer Res 78:748–755
16. Hirata K, Horikoshi N, Aiba K et al (1999) Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. Clin Cancer Res 5:2000–2005
17. Nagashima F, Ohtsu A, Yoshida S et al (2005) Japanese nationwide post-marketing survey of S-1 in patients with advanced gastric cancer. Gastric Cancer 8:6–11
18. Lindeman RD, Tobin J, Shock NW (1985) Longitudinal studies of decline in renal function with age. J Am Geriatr Soc 33:278–285
19. Balducci L, Beghe C (2000) The application of the principles of geriatrics to the management of the older person with cancer. Crit Rev Oncol Hematol 35:147–154
20. Repetto L, Frantino L, Audisio RA et al (2002) Comprehensive geriatric assessment adds information to eastern cooperative oncology group performance status in elderly cancer patients: an italian group for geriatric oncology study. J Clin Oncol 20:494–502
21. Chen H, Cantor A, Meyer J et al (2003) Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer 97:1107–1114
22. Freyer G, Geay JF, Touzet S et al (2005) Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. Ann Oncol 16:1795–1800
23. Monfardini S, Ferrucci L, Fratino L et al (1996) Validation of a multidimensional scale for use in elderly cancer patients. Cancer 77:395–401
24. Extermann M, Hurria A (2007) Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 25:1824–1831
25. Graziano F, Santini D, Testa E et al (2003) A phase II study of weekly cisplatin, 6S-stereoisomer leucovorin and fluorouracil as first-line chemotherapy for elderly patients with advanced gastric cancer. Br J Cancer 89:1428–1432
26. Santini D, Graziano F, Catalano V et al (2006) Weekly oxaliplatin, 5-fluorouracil and folinic acid (OXALF) as first-line chemotherapy for elderly patients with advanced gastric cancer: results of a phase II trial. BMC Cancer 6:125
27. Kim YJ, Kim JH, Park MS et al (2011) Comprehensive geriatric assessment in Korean elderly cancer patients receiving chemotherapy. J Cancer Res Clin Oncol 137:839–847

Int J Clin Oncol
DOI 10.1007/s10147-011-0339-7

ORIGINAL ARTICLE

Adjuvant therapy with imatinib mesylate after resection of primary high-risk gastrointestinal stromal tumors in Japanese patients

Tatsuo Kanda · Toshirou Nishida · Norihito Wada · Osamu Kobayashi · Masakazu Yamamoto · Akira Sawaki · Narikazu Boku · Masato Koseki · Toshihiko Doi · Yasushi Toh · Yoshihiro Kakeji · Toshiro Sugiyama · Yoshito Komatsu · Shojiro Kikuchi · Kyoji Ogoshi · Hitoshi Katai · Kazuhito Miyachi · Seiichi Hirota · Atsushi Ohtsu

Received: 28 April 2011 / Accepted: 5 October 2011

Abstract
Background Imatinib mesylate, a small-molecule tyrosine kinase inhibitor, is currently used for adjuvant therapy of patients who have undergone resection of high-risk gastrointestinal stromal tumors (GISTs). There are no data concerning the efficacy and safety of postoperative adjuvant therapy with imatinib for Japanese or East Asian patients with GIST.
Methods A single-arm, open-label, multicenter trial was conducted in 17 hospitals in Japan. The eligibility criteria included histologically proven primary high-risk GISTs with macroscopic complete resection. Patients were treated with imatinib at a dose of 400 mg/day for 1 year after surgery. The primary endpoint was recurrence-free survival as assessed by Kaplan–Meier analysis. The secondary endpoints were overall survival and safety. This study was registered with ClinicalTrials.gov, number NCT00171977.
Results A total of 64 patients were enrolled between September 2004 and July 2006. The median age of the patients was 59.5 years. Forty-nine (76.6%) patients completed the 1-year treatment, whereas 15 (23.4%) patients did not complete the treatment owing to recurrence, toxicities, and

T. Kanda (✉)
Department of Surgery, Niigata University Medical and Dental Hospital, 1-754 Asahimachi-dori, Chuo-ku, Niigata 951-8520, Japan
e-mail: kandat@med.niigata-u.ac.jp

T. Nishida
Department of Surgery, Osaka University Hospital, Osaka, Japan

N. Wada
Department of Surgery, Keio University Hospital, Tokyo, Japan

O. Kobayashi
Department of Gastrointestinal Surgery, Kanagawa Cancer Center Hospital, Yokohama, Kanagawa, Japan

M. Yamamoto
Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University Hospital, Tokyo, Japan

A. Sawaki
Department of Gastroenterology, Aichi Cancer Center Central Hospital, Nagoya, Aichi, Japan

N. Boku
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

M. Koseki
Department of Surgery, National Hospital Organization Kure Medical Center, Hiroshima, Japan

T. Doi · A. Ohtsu
Division of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan

Y. Toh
Department of Gastroenterological Surgery, National Kyushu Cancer Center, Fukuoka, Japan

Y. Kakeji
Second Department of Gastrointestinal Surgery, Kyushu University Hospital, Fukuoka, Japan

T. Sugiyama
Department of Gastroenterology, Toyama University Hospital, Toyama, Japan

Y. Komatsu
Department of Gastroenterology, Hokkaido University Hospital, Hokkaido, Japan

S. Kikuchi
Division of Digestive Surgery, University Hospital, Kyoto Prefectural University of Medicine, Kyoto, Japan

Published online: 23 November 2011

consent withdrawal. At the median follow-up period of 109 weeks, 20 patients had recurrence. The 3-year recurrence rate was 42.7% (95% confidence interval 29.2–56.3%), which exceeded the expected recurrence rate in this trial. The recurrence-free and overall survival rates at 2 years were 71.1 and 93.7%, respectively. The most frequent adverse drug reaction of any grade was eyelid edema (48.4%), followed by neutropenia (40.6%), leukopenia (39.1%), nausea (39.1%), rash (37.5%), and peripheral edema (37.5%), most of which were mild and manageable.

Conclusions Adjuvant therapy with imatinib at 400 mg/day for 1 year is well tolerated by Japanese patients and possibly reduces the risk of early recurrence of high-risk GISTs.

Keywords Adjuvant therapy · Clinical trial · Gastrointestinal stromal tumor · GIST · Imatinib

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. This tumor is thought to originate from the precursor cells of the interstitial cells of Cajal, intestinal pacemaker cells controlling peristaltic activity. More than 90% of GISTs show expression of KIT kinase (CD117), and the constitutive activation of this protein, which is caused by gene mutations, plays a pivotal role in the pathogenesis of GISTs [1].

The mainstay of treatment for localized, primary GISTs has been surgical resection. Unfortunately, a substantial number of patients develop recurrence even after macroscopically complete resection has been achieved. The risk of recurrence is high particularly in patients with high-risk GISTs, which are large tumors and/or tumors with high mitotic indices: the recurrence probability in this population exceeds 50% at 2 years [2]. Such a high recurrence rate after primary surgical resection underscores the need for a multimodal approach to reduce the risk of recurrence after surgical resection of GISTs.

K. Ogoshi
Department of Gastroenterological Surgery,
Tokai University Hospital, Isehara, Kanagawa, Japan

H. Katai
Gastric Surgery Division, National Cancer Center Hospital,
Tokyo, Japan

K. Miyachi
First Department of Surgery, Dokkyo Medical University
Hospital, Tochigi, Japan

S. Hirota
Department of Surgical Pathology, Hyogo College of Medicine,
Nishinomiya, Hyogo, Japan

Imatinib mesylate is a small-molecule tyrosine kinase inhibitor that is active against BCR-ABL, KIT receptors, and platelet-derived growth factor receptor α (PDGFRA). This molecularly targeted drug shows a potent antitumor effect on GISTs and is now widely recognized as the standard of treatment for patients with unresectable and/or metastatic GISTs [3, 4]. Thus, use of this drug as an adjuvant therapy for patients with high-risk GISTs provided us with a convincing rationale as evidence obtained from clinical oncology of other malignancies accumulates. Adjuvant therapies using effective chemotherapeutic agents have been shown to offer benefits to patients postoperatively [5–7].

Recently, the American College of Surgeons Oncology Group (ACOSOG) have revealed the results of a clinical study concerning imatinib treatment for GIST patients in the adjuvant setting (ACOSOG Z9001 study) [8]. This study was designed as a multicenter, double-blind, placebo-controlled, randomized clinical trial and has shown that 1-year treatment with imatinib significantly improved recurrence-free survival (RFS); the RFS at 1 year was 97.7% in the imatinib-treated group compared with 82.3% in the placebo-treated group. In this study, the completion rate of the adjuvant therapy was not significantly different from that of placebo, demonstrating that 1-year treatment with imatinib is well tolerated by GIST patients who underwent curative surgery. These findings strongly support the recommendation for postoperative adjuvant use of imatinib in GIST patients. However, it remains to be determined whether the results obtained from the phase III study can be applied to East Asian patients as well as patients in western countries, because East Asian patients tend to have a lower body weight and a smaller body surface area than patients in western countries, which may influence their tolerance of imatinib. Actually, it had been empirically known that severe adverse events were frequently experienced during imatinib treatment of Japanese patients with unresectable and metastatic GISTs, and this finding has been recently published [9]. These clinical backgrounds prompted us to obtain clinical evidence concerning adjuvant therapy with imatinib in Japanese GIST patients. Thus, a phase II trial was designed to determine the efficacy and safety of imatinib adjuvant therapy for Japanese GIST patients, which was conducted independently from the phase III trial in the USA (ACOSOG Z9001). Here, we present the results of this single-arm, open-label, multicenter trial.

Patients and methods

Patients

Eligibility criteria required patients to be aged between 20 and 75 years, with the histological diagnosis of primary

high-risk GIST that expressed the KIT protein (CD117) by immunohistochemistry, and having undergone complete resection. KIT expression, tumor sizes, and mitotic indices were determined by the pathologist in each local participating institution and eligibility was determined on the basis of the pathological evaluation in each institution. High-risk GISTs were defined on the basis of the risk classification established by the National Institutes of Health consensus: that is, either a tumor size >5 cm with a mitotic count >5/50 high power fields (HPF), a tumor size >10 cm, or a mitotic count >10/50 HPF [10]. The diagnosis was confirmed by a retrospective central review by a single pathologist (S.H.). In this trial, also eligible were patients who had metastatic deposits if the metastatic tumors were completely excised by the initial surgery for primary tumors. Patients were to be enrolled within 70 days after macroscopic complete resection. Inclusion criteria also included the following: an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; an adequate organ function as indicated by a neutrophil count of 1,500/μL or more, a platelet count of 100,000/μL or more, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels within 2.5 times the upper limit of normal (ULN), a bilirubin level less than 1.5 × ULN, a creatinine level less than 1.5 × ULN, and written informed consent. Patients were not allowed to receive any chemotherapy or radiotherapy for at least 4 weeks before study entry. Also, patients were excluded if they received imatinib therapy prior to the study entry, if they were breastfeeding, or if they had New York Heart Association class 3 or 4 cardiac disease.

The study was approved by the institutional review board of each participating institution, and we obtained written informed consent from all patients.

Study design and procedures

This study was a single-arm, open-label, multicenter phase II trial, aimed to evaluate the efficacy of adjuvant therapy with imatinib in GIST patients. All the eligible patients were assigned to undergo postoperative adjuvant therapy with imatinib. The treatment was started at a dose of 400 mg/day within 84 days after surgical resection and completed after 48-week treatment or confirmation of tumor recurrence. We assessed patients at weeks 2, 4, 6, 8, 12, 16, 20, and 24 and then every 3 months until year 3 with physical examination, complete blood count with differential count, and routine biochemical examinations. Adverse drug reactions were graded on the basis of the National Cancer Institute common terminology criteria for adverse events (version 2.0). The dose was modified for grade 3 and 4 events that were thought to be at least possibly related to treatment. Computed tomography (CT) with intravenous contrast or magnetic resonance imaging (MRI) with intravenous contrast of the abdomen and pelvis were carried out every 3 months for 3 years.

This study was registered with ClinicalTrials.gov, number NCT00171977.

Immunohistochemical and genetic analyses

In the central pathological review of this study, a polyclonal rabbit antibody (A4502; DAKO, Kyoto, Japan) was used for immunohistochemical analysis of KIT (CD117) expression. Mutation analysis of surgically excised tumors was conducted in all patients. Genomic DNA was extracted from formalin-fixed, paraffin-embedded sections of the tumors and *KIT* (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18) were amplified by polymerase chain reaction (PCR). Gene mutations in each exon were analyzed by a direct DNA sequencing technique.

Statistical analysis

The primary endpoint of this study was RFS and the secondary endpoints were overall survival and safety.

RFS was defined as the time from surgery to the development of recurrence or death from any cause. Patients who had not relapsed or withdrew from the trial for any reason other than "condition no longer requires therapy" were censored for analysis at the time of their last tumor assessment. Overall survival was defined as the time from surgery to death from any cause. The date of death was included in follow-up data. Patients who did not die were censored on the last date they were known to be alive. Both endpoints were estimated by the Kaplan–Meier method. All analyses were performed using Statistical Analysis Software (version 8.0; SAS Institute, Cary, NC, USA).

In this study, the single-arm study design was adopted owing to the shortage of available GIST patients in Japan. As the historical data on RFS were limited, we calculated the required patient number on the basis of the 3-year recurrence rate of 40% for patients with a maximum tumor diameter of ≥5 cm and a mitotic count of ≥1/10 HPF, which was only available at that time. The expected recurrence rate for patients treated with imatinib was assumed to be 20%, approximately half the above rate, and the clinically meaningful difference was 20%. By applying Fleming's single-stage method at alpha = 0.025 (one-sided) with 90% power, we determined the required sample size to be 55 patients. Therefore, the target sample size was set to 60 patients including dropouts. This sample size also enabled us to detect an adverse event (AE) of 5% incidence with 95% probability. This detection was based on the idea of "the rule of 3": that is, the probability of none of the 60

patients developing AE of 5% incidence was calculated using the following equation: $1 - (1–0.05)^{60} \geq 0.95$ [11].

Results

Demographics and clinicopathological features

A total of 64 patients were enrolled between September 2004 and July 2006 in 17 hospitals in Japan. All patients were eligible, and their diagnosis of KIT-positive GIST was confirmed by central pathological review. Their baseline demographics and clinicopathological features are summarized in Table 1. The median size of tumors was 9.0 cm, and the median mitotic count was 15/50 HPF.

Table 1 Demographics and clinicopathological features ($N = 64$)

	N (%)
Sex	
Men	41 (64.1)
Women	23 (35.9)
Age (years)	
Median	59.5
Range	27–74
ECOG performance status	
0	56 (87.5)
1	8 (12.5)
Tumor origin	
Esophagus	1 (1.6)
Stomach	40 (62.5)
Small intestine	16 (25.0)
Colon	2 (3.1)
Rectum	5 (7.8)
Tumor size (cm)	
>2, ≤5	13 (20.3)
>5, ≤10	25 (39.1)
>10	26 (40.6)
Median	9.0
Range	2.8–30.0
Mitotic count[a] (/50 HPF)	
≤5	6 (9.4)
>5, ≤10	16 (25.0)
>10	39 (60.9)
Unknown	3 (4.7)
Median	15.0
Range	0–149
Condition of high risk	
Tumor size, mitotic count	
>5 cm, >5/50 HPF	12 (18.8)
>10 cm, any mitotic rate	13 (20.3)
Any size, >10/50 HPF	27 (42.2)
>10 cm, >10/50 HPF	12 (18.8)

ECOG Eastern Cooperative Oncology Group, *HPF* high power fields

[a] Based on each institution

Feasibility and safety

Forty-nine (76.6%) patients completed the 1-year treatment whereas 15 (23.4%) patients stopped the treatment prematurely. The reasons for discontinuation in the 15 patients were recurrence ($N = 2$), toxicities ($N = 10$), and consent withdrawal related to toxicities ($N = 3$).

Adverse events related to imatinib treatment were reported in all patients, many of which were of grade 1 or 2 and well tolerated. In Table 2, we summarize the adverse drug reactions that occurred in more than 10% of the patients. Of these, the most frequent adverse drug reaction was eyelid edema (48.4%), followed by neutropenia (40.6%), leukopenia (39.1%), nausea (39.1%), rash (37.5%), and peripheral edema (37.5%). Grade 3 or higher adverse drug reactions occurred in 22 patients (34.4%), with neutropenia (14.1%) being the most frequent adverse drug reaction, followed by leukopenia (4.7%), lymphopenia (3.1%), and rash (3.1%). Four patients experienced grade 4 adverse events that included neutropenia, hypertrophic cardiomyopathy, prostate cancer, and suicidal ideation. In addition, one patient died by suicide.

Efficacy

We noted a total of 20 events occurring in the 64 patients at the median follow-up period of 109 weeks (Fig. 1). The recurrence rate at 3 years was 42.7% [95% confidence interval (CI) 29.2–56.3%], which exceeded the expected recurrence rate in this phase II study.

The Kaplan–Meier-estimated 1-, 2-, and 3-year RFS rates were 94.7% (95% CI 88.9–100.0%), 71.1% (95% CI 58.5–83.7%), and 57.3% (95% CI 43.7–70.8%), respectively. Median RFS time was not reached at the time of this analysis.

The RFS curve showed a biphasic slope and appeared to decline faster at approximately 72 weeks after surgery. Two patients showed recurrence during the 1-year treatment period: one was a patient with a *KIT* exon 9-mutated small-bowel GIST and the other was a stomach GIST patient in whom *KIT* or *PDGFRA* mutation was not found. Both of the patients had liver metastases.

As regards overall survival, 8 deaths were recorded. Four patients died of GIST and the remaining 4 died of other diseases. The 1-, 2-, and 3-year overall survival rates were 96.8, 93.7, and 87.1%, respectively (Fig. 2).

As there has been accumulating evidence that gastric GIST patients show better prognosis than patients with intestinal GISTs [12], we compared the RFS of 40 patients

Table 2 Adverse drug reactions that were found in 10% or more of 64 eligible patients ($N = 64$)

System organ class[a]	*N* (%)				
Preferred term[a]	Grade 1	Grade 2	Grade 3	Grade 4	Any grade
Any adverse effect	9 (14.1)	33 (51.6)	17 (26.6)	5 (7.8)	64 (100)
Gastrointestinal disorders	35 (54.7)	11 (17.2)	3 (4.7)	0	49 (76.6)
Nausea	20 (31.3)	4 (6.3)	1 (1.6)	0	25 (39.1)
Diarrhea	17 (26.6)	3 (4.7)	1 (1.6)	0	21 (32.8)
Vomiting	7 (10.9)	1 (1.6)	1 (1.6)	0	9 (14.1)
Skin and subcutaneous tissue disorders	22 (34.4)	20 (31.3)	2 (3.1)	0	44 (68.8)
Rash	9 (14.1)	13 (20.3)	2 (3.1)	0	24 (37.5)
Face edema	15 (23.4)	8 (12.5)	0	0	23 (35.9)
General disorders and administration site conditions	19 (29.7)	19 (29.7)	1 (1.6)	0	39 (60.9)
Peripheral edema	17 (26.6)	7 (10.9)	0	0	24 (37.5)
Malaise	11 (17.2)	8 (12.5)	1 (1.6)	0	20 (31.3)
Eye disorders	32 (50.0)	6 (9.4)	0	0	38 (59.4)
Eyelid edema	27 (42.2)	4 (6.3)	0	0	31 (48.4)
Blood and lymphatic system disorders	4 (6.3)	20 (31.3)	9 (14.1)	1 (1.6)	34 (53.1)
Neutropenia	1 (1.6)	16 (25.0)	8 (12.5)	1 (1.6)	26 (40.6)
Leukopenia	1 (1.6)	21 (32.8)	3 (4.7)	0	25 (39.1)
Lymphopenia	0	6 (9.4)	2 (3.1)	0	8 (12.5)
Thrombocytopenia	8 (12.5)	0	0	0	8 (12.5)
Eosinophilia	6 (9.4)	1 (1.6)	0	0	7 (10.9)
Investigations	14 (21.9)	13 (20.3)	0	0	27 (42.2)
Hemoglobin level decreased	8 (12.5)	6 (9.4)	0	0	14 (21.9)
Aspartate aminotransferase level increased	7 (10.9)	1 (1.6)	0	0	8 (12.5)
Alanine aminotransferase level increased	4 (6.3)	3 (4.7)	0	0	7 (10.9)
Musculoskeletal and connective tissue disorders	20 (31.3)	0	0	0	20 (31.3)
Muscle cramp	16 (25.0)	0	0	0	16 (25.0)
Metabolism and nutrition disorders	9 (14.1)	4 (6.3)	5 (7.8)	0	18 (28.1)
Anorexia	10 (15.6)	2 (3.1)	1 (1.6)	0	13 (20.3)

[a] Adverse events were classified using Medical Dictionary for Regulatory Activities (MedDRA/J ver. 7.0)

with gastric GIST with that of 24 patients with GISTs of other origins, and the results were found to be similar (Fig. 3).

Genetic analysis

Somatic mutation analyses of primary tumors were conducted in 62 patients. In the remaining 2, PCR products were not obtained because of low quality of pathological specimens. Of the 62 analyzable tumors, *KIT* or *PDFGRA* mutations were found in 59 patients. The genetic profile of the 64 patients enrolled is shown in Table 3.

As tumors harboring the gene mutations in exon 11 of *KIT* and exon 12 of *PDGFRA* show a much higher in-vitro sensitivity to imatinib than tumors having other genotypes [13], we compared RFS between the group of patients with the above-mentioned gene mutations and that with other mutations (Fig. 4). The subgroup analysis failed to show clearly the features of RFS curves of the 2 groups, because of underpowered analysis owing to the limited number of patients.

Discussion

Feasibility is clinically more important in postoperative adjuvant therapy than in the treatment of recurrent tumors, because adjuvant therapy is administered immediately after surgery, making it difficult for patients to tolerate. When the present study was planned, it was questioned whether or not the safety and feasibility of postoperative adjuvant therapy under the special condition, i.e., after gastrointestinal surgery for GIST, could be ensured in Asian patients who have smaller body sizes than European and American patients. To answer this clinical question, this phase II study was performed.

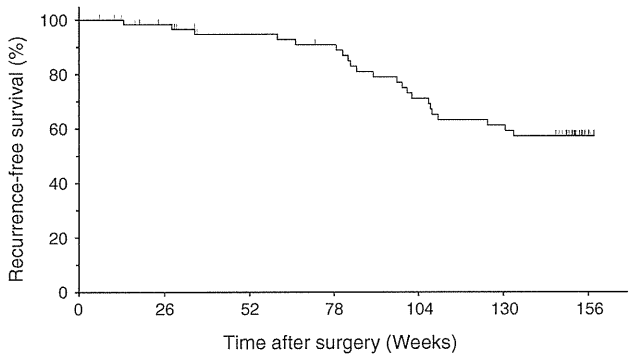

Fig. 1 Kaplan–Meier estimates of recurrence-free survival (RFS). The median RFS time was not reached during the study. The Kaplan–Meier-estimated 1-, 2-, and 3-year RFS rates were 94.7% (95% CI 88.9–100.0%), 71.1% (95% CI 58.5–83.7%), and 57.3% (95% CI 43.7–70.8%), respectively

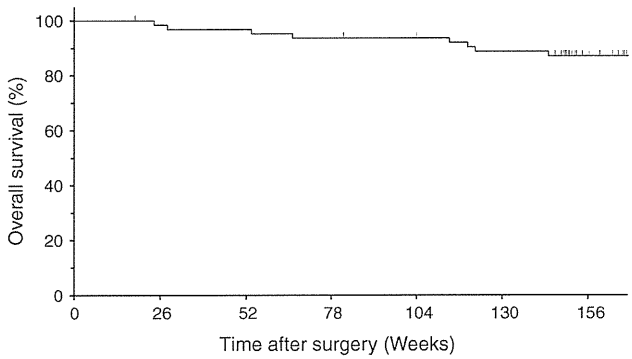

Fig. 2 Kaplan–Meier estimates of overall survival. Eight patients had had an event. The 1-, 2-, and 3-year overall survival rates were 96.8% (95% CI 92.5–100.0%), 93.7% (95% CI 87.6–99.7%), and 87.1% (95% CI 78.7–95.4%), respectively

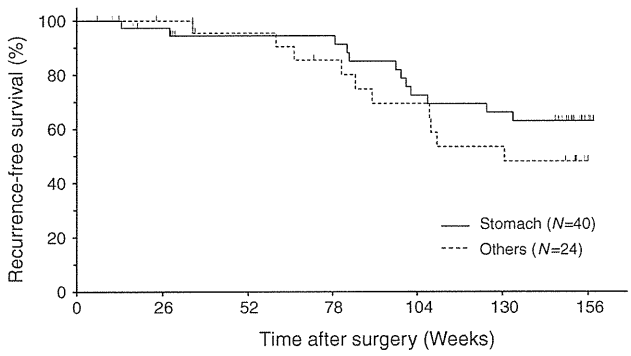

Fig. 3 Kaplan–Meier estimates of recurrence-free survival (RFS) depending on primary tumor origin. The RFS times of patients with gastric GIST ($N = 40$, *solid line*) and patients with GISTs of other origins ($N = 20$, *dotted line*) are shown. The median RFS time of gastric GIST patients was not reached during the study, whereas that of the patients with GISTs of other origins was 130 weeks

When we designed this trial in 2003, no data on RFS in Japanese patients with high-risk GISTs were available. Thus, as an alternative, we used the patients' recurrence rates at 3 years for calculation of the sample size of this study. Meanwhile, we determined RFS to be the primary endpoint in this study, considering that it would be highly informative and easier to compare with the results that would be published soon by ongoing international phase III trials on adjuvant therapy with imatinib. However, the mismatch between sample size calculation and primary endpoint hindered the determination of the appropriate follow-up time and consequently made it impossible to scientifically evaluate the efficacy of the adjuvant therapy in the present phase II study. Although these deficiencies in the study design have markedly lowered the quality of this clinical trial, the present multicenter study is still valuable as it provides clinically important findings regarding adjuvant therapy with imatinib for Japanese GIST patients.

Table 3 Oncogenic mutations ($N = 64$)

	N (%)
KIT exon 9	6 (9.4)
KIT exon 11	49 (76.6)
KIT exon 17	1 (1.6)
PDGFRA exon 12	2 (3.1)
PDGFRA exon 18	1 (1.6)
Wild type	3 (4.7)
Unknown	2 (3.1)

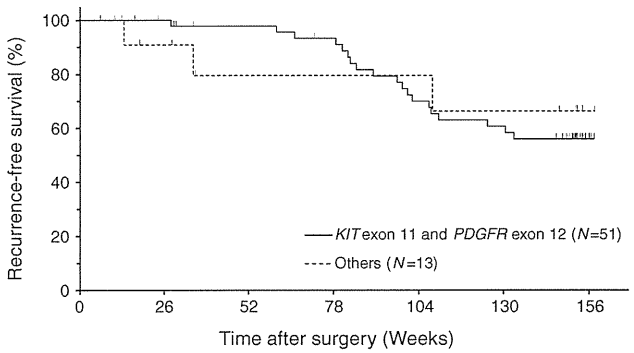

Fig. 4 Kaplan–Meier estimates of recurrence-free survival (RFS) depending on genotype. The RFS time of the *KIT* exon 11 and *PDGFRA* exon 12 mutation group ($N = 51$, *solid line*) and other mutations group ($N = 13$, *dotted line*) are shown. The median RFS time was not reached during the study

In the present study, 64 high-risk GIST patients who underwent complete resection were enrolled and treated with imatinib at 400 mg/day for 1 year. Of these, 49 (76.6%) completed the 1-year protocol therapy. ACOSOG has recently reported the results of a randomized controlled study (Z9001) of postoperative adjuvant therapy with imatinib [8]. The Z9001 study is a large-scale, randomized controlled study of patients with primary GISTs, and is the most reliable of the clinical studies of adjuvant therapy with imatinib that have been published to date. In that