operation between 2000 and 2007. Patients with obvious malignant pleural effusion or with Stage IV disease were excluded before the registration. A total of 3493 patients were registered from 12 institutes in which PLC had been routinely examined. After excluding the patients against eligible criteria (small cell carcinoma, 40; low-grade malignancy, 4; multiple primary lung cancer or pulmonary metastasis, 20; M1a or M1b, 62; incomplete data, 136), a total of 3231 patients were included in the study.

Methods

PLC was performed by washing the thoracic cavity with 20–500 ml of physiological saline immediately after opening the thoracic cavity during surgery; a 10–20 ml of specimen was collected for cytological examination. Actually, in most institutes, physiological saline of ≤100 ml was used for lavage fluid. Washing with 500 ml, which was used in two institutes, may increase the false-negative findings due to the over-dilution. However, according to the result of preliminary analysis that incidence of positive PLC findings per each institutes had no statistical difference ($P = 0.208$), we accepted the registration from the 500 ml institutes. We recommend the amount of lavage fluid not to exceed 100 ml. In this study, a routine radical operation for lung cancer, with mediastinal lymph node dissection conforming to the *General Rule for Clinical and Pathological Record of Lung Cancer* (6th edition) by the Japanese Lung Cancer Society [15], was performed in all patients irrespective of their PLC results. In cases where parietal pleural invasion was identified, combined resection of the pleura and chest wall, if necessary, was performed. Postoperative pathological evaluation was performed by each institute's pathologist to determine the histology, tumour size and pathological TNM. pleural invasion was also evaluated by the pathologist as a PL score ranging from PL0 to PL3 as follows: PL0, tumour within the subpleural lung parenchyma; PL1, invasion beyond the elastic layer; PL2, invasion to the pleural surface; PL3, invasion to the parietal pleura [1]. Data were collected from databases, including the result of PLC, age, gender, survival time, dead or alive (all death or censored), operative procedure, actual disease-free time, site of recurrence and information about adjuvant chemotherapy. The pathological T (pT) and pathological N (pN) scores were converted to the new 7th Edition TNM Classification [16, 17], but some stage migration of the N score could not be avoided because of the discontinuity between the Naruke map and the Rusch–Asamura map [18].

Statistical analyses

In a background analysis, age, gender, histology, pathological stage (p-Stage), pT, pN and PL scores were compared between the PLC-positive (PLC^+) group and the PLC-negative (PLC^-) group. Differences were assessed statistically using a *t*-test for the numerical variables and a χ^2 test for the categorical variables. A *P*-value of <0.05 was considered to be statistically significant. Survival analysis was performed first with the entire cohort; next, subset analyses were performed on the histology (adenocarcinoma, squamous cell carcinoma and others), p-Stage, pT, pN and PL scores. Survival curves were generated via the Kaplan–Meier method, and statistical differences between the PLC^+ group and PLC^- group were evaluated by the logrank test. A multivariate analysis using a Cox proportional hazard model (Cox analysis) was also performed to evaluate the significance of prognostic factors (PLC, age, gender, tumour size, pN and PL scores), and the hazard ratio, likelihood ratio χ^2 statistic (χ^2) and *P*-value (probability > χ^2) were estimated. All statistical analyses were performed using StatMate IV software (ATMS, Tokyo, Japan) or JMP 8.0 software (SAS Institute Japan, Tokyo, Japan).

Integration of the pleural lavage cytology-positive findings with the existing staging factors

After the evaluation of the six prognostic factors, integration of the PLC^+ findings with the existing staging factors was attempted for convenience of TNM staging. According to the results of the subset analysis and theoretical considerations, integration of the PLC^+ findings with the PL score was considered to be most reasonable. Seeking the appropriate PL score matching to the PLC^+ findings, the Cox analysis was re-estimated using a corrected PL score by replacing the score of underestimated cases with a higher score in a gradual manner (PL1, PL2 and then PL3). The

Table 1: Patient characteristics of studied groups

	PLC^+ group	PLC^- group	*P*-value
Age [mean (SD)]	66.9 (10.2)	65.6 (9.9)	0.118
Gender[a]			
Male	81 (54.7%)	1929 (62.6%)	0.054
Female	67 (45.3%)	1154 (37.4%)	
Histology[a]			
Adenocarcinoma	111 (75.0%)	2137 (69.3%)	0.015[b]
Adenosquamous cell carcinoma	6 (4.1%)	83 (2.7%)	
Squamous cell carcinoma	22 (14.9%)	752 (24.4%)	
Large cell carcinoma	5 (3.4%)	88 (2.9%)	
LCNEC	2 (1.4%)	9 (0.3%)	
Others	2 (1.4%)	14 (0.5%)	
Pathological stage[a]			
IA	24 (16.2%)	1114 (36.1%)	<0.001[b]
IB	51 (34.5%)	924 (30.0%)	
IIA	16 (10.8%)	343 (11.1%)	
IIB	11 (7.4%)	184 (6.0%)	
IIIA	43 (29.1%)	492 (16.0%)	
IIIB	3 (2.0%)	26 (0.8%)	
Pathological T score[a]			
T1a	15 (10.1%)	772 (25.0%)	<0.001[b]
T1b	13 (8.8%)	494 (16.0%)	
T2a	86 (58.1%)	1350 (43.8%)	
T2b	9 (6.1%)	147 (4.8%)	
T3	20 (13.5%)	273 (8.9%)	
T4	5 (3.4%)	47 (1.5%)	
Pathological N score[a]			
N0	91 (61.5%)	2298 (74.5%)	<0.001[b]
N1	15 (10.1%)	351 (11.4%)	
N2	41 (27.7%)	422 (13.7%)	
N3	1 (0.7%)	12 (0.4%)	
Pathological PL score[a]			
PL0	44 (29.7%)	1739 (56.4%)	<0.001[b]
PL1	45 (30.4%)	917 (29.7%)	
PL2	43 (29.1%)	246 (8.0%)	
PL3	16 (10.8%)	181 (5.9%)	

PLC: pleural lavage cytology; PLC^+: PLC-positive group; PLC^-: PLC-negative group; LCNEC: large cell neuroendocrine carcinoma.
[a]Expressed by the number of the cases with its ratio.
[b]Statistical difference was confirmed with $P < 0.05$.

reliability of each Cox proportional hazard model was evaluated by the χ^2 and *P*-value with regard to the whole model and to the PL score. Since the *P*-values were too small to compare with each other, χ^2 was used in this instance. The model with the largest χ^2 has the smallest *P*-value and, therefore, is the most reliable model.

RESULTS

The incidence of PLC$^+$ findings was 4.58% (148/3231). In a background analysis, histology, pathological stage (p-Stage), pT, pN and PL scores had significant differences between the groups (Table 1). It was suspected that the PLC$^+$ group consisted of patients whose cancer had advanced to a particular stage. Regarding to the higher incidence of N2 disease in the PLC$^+$ group, cancer may migrate the lymphatic channels of the pleura and may cause the lymph node metastasis. However, the recurrence rate associated with the mediastinal-supraclavicular lymph node enlargement had no statistical difference ($P = 0.450$) between the PLC$^+$ group and the PLC$^-$ group, which was estimated to be 8.8 and 6.6%, respectively. The survival curve of the PLC$^+$ group was significantly worse than that of the PLC$^-$ group in terms of both the overall survival (OS) and disease-free survival (DFS) (Fig. 1). Differences in the subset analysis are shown in Table 2, and DFS curves for each p-Stage and each PL score are shown in Figs 2 and 3, respectively. In Stages IA and IB, the survival curves of the PLC$^+$ group were significantly worse than those of the PLC$^-$ group. As for the PL score, the survival curves of the PLC$^+$ group were also worse in the PL0 and PL1 groups. However, differences were not observed in the PL2 and PL3 groups. These findings suggested that the PLC$^+$ patients should not be included in these earlier stages.

Table 2: Differences in survival between the PLC$^+$ group and the PLC$^-$ group

	Overall survival	Disease-free survival
Histology		
Adenocarcinoma	$P < 0.001$*	$P < 0.001$*
Squamous cell carcinoma	$P = 0.496$	$P = 0.188$
Others	$P = 0.877$	$P = 0.837$
Pathological stage		
IA	$P = 0.045$*	$P < 0.001$*
IB	$P = 0.010$*	$P < 0.001$*
IIA	$P = 0.821$	$P = 0.270$
IIB	$P = 0.004$*	$P = 0.003$*
IIIA	$P = 0.984$	$P = 0.993$
IIIB	$P = 0.984$	$P = 0.149$
Pathological T score		
T1a	$P = 0.928$	$P = 0.025$*
T1b	$P = 0.094$	$P = 0.009$*
T2a	$P = 0.023$*	$P < 0.001$*
T2b	$P = 0.668$	$P = 0.923$
T3	$P = 0.273$	$P = 0.151$
T4	$P = 0.204$	$P = 0.783$
Pathological N score		
N0	$P < 0.001$*	$P < 0.001$*
N1	$P = 0.281$	$P = 0.023$*
N2+3	$P = 0.472$	$P = 0.351$
Pathological PL score		
PL0	$P = 0.129$	$P = 0.013$*
PL1	$P = 0.026$*	$P < 0.001$*
PL2	$P = 0.184$	$P = 0.079$
PL3	$P = 0.948$	$P = 0.875$

Expressed by *P*-values of the logrank test.
PLC: pleural lavage cytology; PLC$^+$: PLC-positive group; PLC$^-$: PLC-negative group.
*Statistical difference was confirmed with $P < 0.05$.

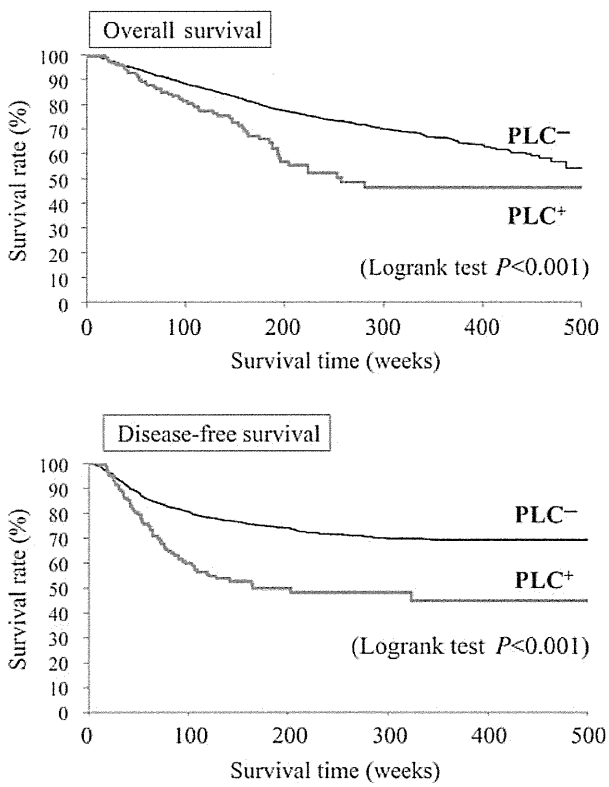

Figure 1: Comparison of survival curves by PLC status. Overall survival curves are shown in the top panel and DFS curves in the bottom panel. Statistical differences (*P*-values) were calculated by the logrank test. PLC: pleural lavage cytology; PLC$^+$: PLC-positive group; PLC$^-$: PLC-negative group.

In an analysis of recurrent cases, the incidence of a malignant pleural effusion or obvious pleural dissemination (pleuritis carcinomatosa) was 17.6% (26/148) in the PLC$^+$ group, compared with 2.8% (86/3083) in the PLC$^-$ group, a significant difference ($P < 0.001$). However, no difference was apparent with regard to sites of distant metastasis. For this reason, it was concluded that PLC$^+$ findings was a preliminary stage of a malignant pleural effusion.

Among the six variables analysed by Cox analysis, all were statistically significant in terms of OS and DFS (Table 3). PLC$^+$ findings were confirmed as a significantly poor prognostic factor in both OS ($P = 0.016$) and DFS ($P = 0.026$). However, it would be more convenient if the PLC$^+$ findings were integrated with one of the existing TNM staging factors. A total of 89 cases (60.1%) with PLC$^+$ findings had been diagnosed as either PL1 or PL0, which the subset analysis showed to be underestimations of the disease stage. To find the accurate PL score for positive PLC findings, the Cox analysis was re-estimated using the PL score upgraded stepwise. The χ^2 regarding to the whole model reached its maximum value by a correction to PL3 in both OS (uncorrected, PL2, PL3; 654.67, 658.99, 659.04) and DFS

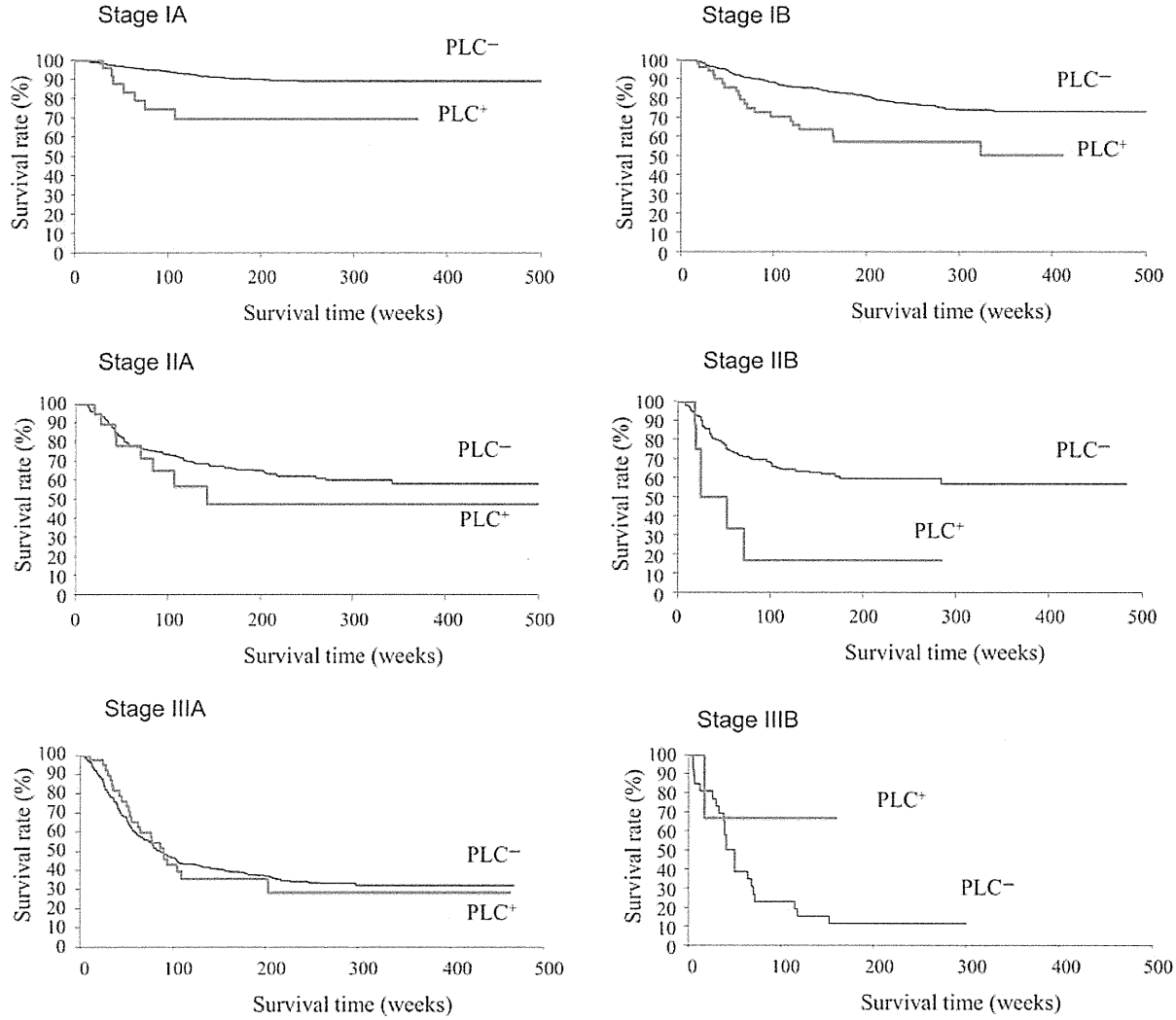

Figure 2: Comparison of DFS curves by pathological stage. Statistical differences (*P*-values) were calculated by the logrank test. PLC: pleural lavage cytology; PLC^+: PLC-positive group; PLC^-: PLC-negative group.

(uncorrected, PL2, PL3; 600.56, 609.28, 609.84). Conversion of the PLC^+ findings to PL3 (=T3) was, therefore, considered to be most appropriate. DFS curves that were re-estimated using the corrected PL score are shown in Fig. 4 to demonstrate the efficacy of correction.

DISCUSSION

The previously reported incidence of PLC^+ findings ranges from 2.7 to 41.7% [2–14]. However, restricting to the papers of large series, the incidence of PLC^+ findings was found to be within the range of 3–6%. PLC^+ findings were reasonably estimated to be 4.58% in our study. Although the survival differences between the PLC^+ and PLC^- groups are obvious, these differences may not have been due only to the sequelae of PLC^+ findings, because many of the other patient characteristics were also significantly different. For this reason, a Cox analysis was performed. All of the six variables analysed were statistically significant and PLC^+ findings were confirmed as a significantly poor prognostic factor. As for the results of the Cox analysis, many investigators [2, 4, 7, 8, 10, 12, 14] have reported that PLC^+ findings are an independent prognostic factor in lung cancer. However, their analysed explanatory variables are inconsistent. Above all, pN, which is widely believed to be the most important prognostic factor, is not included in many studies [2, 4, 7, 8, 10]. In some study, it is converted to a much rougher score, such as 'N0 vs. N1–3' [12]. In our study, the explanatory variables were simplified into two categories, one concerning the life expectancy (age and gender) and the other concerning the tumour growth (tumour size, pN and PL score); p-Stage and pT were not included because these factors may depend on other factors. We used the raw values of pN and PL score. If either of these scores was excluded from the explanatory variables, PLC^+ findings acquire a much smaller *P*-value ($P = 0.001$/OS without pN, $P < 0.001$/OS without PL score, $P < 0.001$/DFS without pN, $P < 0.001$/DFS without PL score) and will be regarded as a much more important prognostic factor. However, this is nothing more than a statistical artefact. The impact of PLC^+ findings should not be overstated. We were simply analysing a particular stage of cancer progression.

The extent of pleural invasion is expressed by a pleural invasion score ranging from PL0 to PL3 and is considered to be useful in

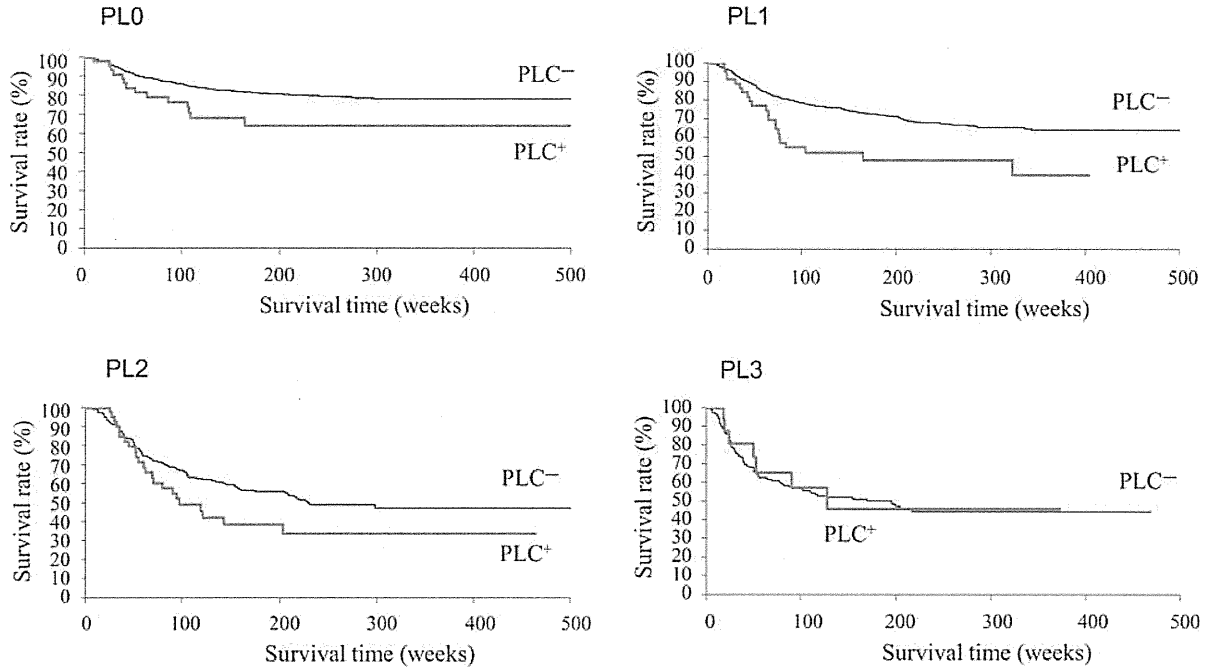

Figure 3: Comparison of DFS curves by the PL score. Statistical differences (*P*-values) were calculated by the logrank test. PLC: pleural lavage cytology; PLC⁺: PLC-positive group; PLC⁻: PLC-negative group.

Table 3: Results of the Cox analysis for overall survival and DFS

Factors	Hazard ratio	Likelihood ratio, χ^2	*P*-value
PLC⁺		5.848 (4.930)	0.016 (0.026)
PLC⁺/PLC⁻	1.436 (1.361)		
Age	1.037 (1.008)	83.419 (4.653)	<0.001 (0.031)
Gender		79.221 (9.458)	<0.001 (0.002)
Male/Female	2.107 (1.265)		
Tumour size	1.014 (1.012)	47.090 (34.032)	<0.001 (<0.001)
N score		227.301 (326.769)	<0.001 (<0.001)
N1/N0	2.036 (2.333)		
N2/N0	3.591 (4.546)		
N3/N0	7.253 (6.579)		
PL score		46.667 (46.140)	<0.001 (<0.001)
PL1/PL0	1.116 (1.343)		
PL2/PL0	1.695 (1.810)		
PL3/PL0	2.079 (2.001)		

Results for DFS data are shown in parentheses.
Cox analysis: multivariate analysis using the Cox proportional hazard model; PLC: pleural lavage cytology; PLC⁺: PLC-positive group; PLC⁻: PLC-negative group.

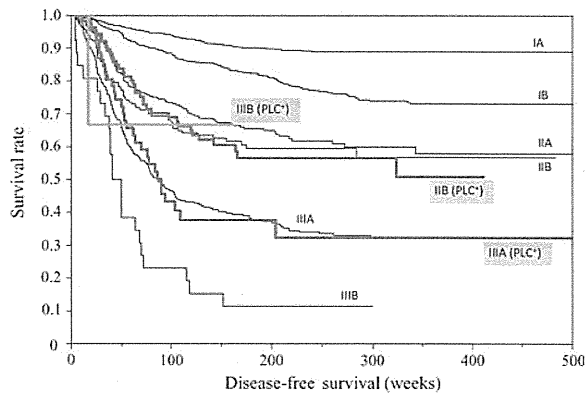

Figure 4: DFS curves after re-staging of the PLC⁺ patients, shown in comparison with that of the PLC⁻ patients. PLC: pleural lavage cytology; PLC⁺: PLC-positive; PLC⁻: PLC-negative; IIB (PLC⁺): Stage IIB in the PLC-positive group; IIIA (PLC⁺): Stage IIIA in the PLC-positive group; IIIB (PLC⁺): Stage IIIB in the PLC-positive group.

predicting prognosis [1]. PL3 is classified as T3 in the TNM classification; recently, PL1 and PL2 were classified as T2a or T2b (depending on tumour size) in the 7th Edition TNM classification [16, 17]. Moreover, in the 7th Edition TNM classification system, the classification of a malignant pleural effusion (pleuritis carcinomatosa) increased from T4 to M1a [16, 17] because of its vicious prognosis. Before the appearance of a pleural effusion, occult (microscopic) dissemination must occur. Although this stage is not currently evaluated, it is detectable by the cytological examination of the pleural cavity, such as via PLC. Theoretically, patients with PLC⁺ findings must be given a score of PL2 or higher because the cancer cells were exfoliated from the lung surface. However, 60.1% of the cases had been diagnosed as either PL1 or PL0 in our study. There is a discrepancy between the theory and clinical data. To evaluate the reliability of the staging, subset analysis was performed. In Stages IA and IB, the survival curves of the PLC⁺ group were significantly worse than those of the PLC⁻ group. As for the PL score, the survival curves of the PLC⁺ group were also worse in the PL0 and PL1 groups. These findings suggested that the PLC⁺ patients should not be included in these stages; instead, they should be classified in more advanced stages. As for the cause of discrepancy in the PL score, two possible explanations are conceivable: (i) cancer cells in the pleural cavity came from another origin, for example, exudation from the

lymphatic channels or nodes; (ii) diagnosis of PL0 or PL1 was made using inappropriate section of histopathological specimen, for example, in the case with deep pleural indentation. The former is a most likely explanation, but it cannot be a single credible cause, because the ratio of N1–2 patients per PL0–1 patients in the PLC^+ group was only 31% in our data. We cannot get farther information because of the limitation of retrospective study. Although cancer cells in the pleural cavity do not always originate from the lung surface, microscopic dissemination should be recognized as a preliminary stage of the malignant pleural effusion. This is the reason why we proposed the re-staging by PLC^+ findings.

Although the PLC^+ findings were confirmed as a significantly poor prognostic factor in the Cox analysis, it would be more convenient if the PLC^+ findings were integrated with one of the existing TNM staging factors. Integration of PLC^+ findings into the PL score may positively contribute to the precise diagnosis of cancer advancement and, therefore, will be useful in evaluating its prognosis. Scoring PLC^+ findings as PL3 (=T3) should be a reasonable method to express the stage between PL2 (=T2a–b) and T4 (=M1a).

Standard operation for lung cancer should not be given up because of the positive findings of PLC. The DFS of the PLC^+ patients, whose stages were re-staged to be either IIB (T3N0) or IIIA (T3N1 and T3N2), were almost equal with that of the ordinary (PLC^- group) Stage IIB or IIIA patients. Their survival is much better than that of the patients with malignant pleural effusion. Although we could not prove the efficacy of adjuvant therapy, due to the retrospective clinical data analysis, adjuvant chemotherapy will be indispensable. Intra-operative intra-pleural administration of hypotonic cysplatin [19] is a procedure of great interest. But farther investigations will be necessary to establish its efficacy.

CONCLUSION

Examining PLC in clinical practice is useful for detecting occult pleural dissemination before the appearance of a malignant pleural effusion. Evidence of PLC^+ findings should be treated as supplemental information to the precise diagnosis of PL score. Scoring PLC^+ findings as PL3 (=T3) was appropriate. However, standard operation should not be given up because of the positive PLC findings. The corrected survival curves of the PLC^+ group were almost equal with that of the ordinary stage IIB or IIIA patients.

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Conflict of interest: none declared.

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Review Article: Study Group

Past and Present Achievements, and Future Direction of the Gastrointestinal Oncology Study Group (GIOSG), a Division of Japan Clinical Oncology Group (JCOG)

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Initially, Gastrointestinal Study Group in Japan Clinical Oncology Group (GIOSG/JCOG) focused on gastric cancer. In 1980s, fluoropyrimidine, cisplatin and mitomycin C were key drugs. A randomized Phase II trial (JCOG8501) comparing futrafur plus mitomycin C and uracil plus futrafur and mitomycin C showed a higher response rate of uracil plus futrafur and mitomycin C than futrafur plus mitomycin C. From the results of two Phase II trials of etoposide, adriamycin and cisplatin, and cisplatin plus 5-fluorouracil, uracil plus futrafur and mitomycin C and cisplatin plus 5-fluorouracil were adopted for the test arms of the Phase III trial (JCOG9205) comparing with continuous infusion of 5-fluorouracil as a control arm. Neither cisplatin plus 5-fluorouracil nor uracil plus futrafur and mitomycin C showed a survival benefit over continuous infusion of 5-fluorouracil. In late 1990s, new agents, irinotecan and S-1, were developed for gastric cancer in Japan. GIOSG conducted a Phase III trial (JCOG9912) investigating superiority of irinotecan plus cisplatin and non-inferiority of monotherapy with S-1 compared with continuous infusion of 5-fluorouracil, and S-1 succeeded in showing non-inferiority. Then, SPIRITS trial showed a survival benefit of S-1 plus cisplatin over S-1, resulting in the establishment of a standard care for advanced gastric cancer in Japan. GIOSG have merged with Gastric Cancer Study Group as the Stomach Cancer Study Group (SCSG) from 2011. Recent progress in the development of new drugs has been remarkable. From the point of the roles shared with many other study groups for clinical trials, including registration trials of new drugs conducted by pharmaceutical companies, SCSG should recognize its role and conduct clinical trials with high quality for establishing new standard treatment.

Key words: Gastrointestinal Oncology Study Group – Japan Clinical Oncology Group – esophageal cancer – gastric cancer – pancreatic cancer, colorectal cancer

INTRODUCTION

In Japan, there are several clinical trial groups. Japan Clinical Oncology Group (JCOG) is a clinical study group in which many multi-institutional clinical trials have been conducted mainly by the support of research aid from the Ministry of Health, Labour and Welfare in Japan. While other clinical trial groups such as Hokkaido Gastrointestinal Cancer Study Group (HGCSG), Tohoku Clinical Oncology Research and Education Society (T-CORE), Japan Clinical Cancer Research Organization (JACCRO), Tokyo Cooperative Oncology Group (TCOG), Chubu Clinical Oncology Group (CCOG), Epidemiological and Clinical Research Information Network (ECRIN), West Japan

Oncology Group (WJOG), Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG), Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC), Kyushu Study Group of Clinical Cancer (KSCC), etc. have also been contributing to establish new evidences for gastrointestinal malignancy, the Gastrointestinal Oncology Study Group (GIOSG) was one of the oldest three study groups dedicated to medical oncology at the beginning of JCOG and has been conducting clinical trials of gastrointestinal malignancy.

Table 1 shows the summary of clinical trials conducted by GIOSG (1–20). In late 1980s, GIOSG focused on gastric cancer and conducted a several Phase II trials (1–4). In early 1990s, it could launch the first Phase III trial (JCOG9205) (5), although its sample size was small. And then, GIOSG could complete a large Phase III trial (JCOG9912) (13). In the twenty-first century, GIOSG challenged to difficult clinical trials [JCOG0106 (14) and 0407 (15)] for gastric cancer patients with severe peritoneal metastasis, who are usually excluded from clinical trials especially for new drug approval, meaning that new standard treatment, including new agents, can hardly be applied to these patients. Along with these clinical trials, GIOSG has been continuing to conduct translational researches to find predictive marker for chemotherapy effects using the archived tissues of the patients enrolled to JCOG9001 (21), 9205 (22) and 9912 (23,24). Recently, GIOSG has expanded its activity for colorectal cancer [JCOG9703 (9) and 0208-DI], esophageal cancer [JCOG9906 (10), 9908-DI (11) and 0508 (18)], pancreatic cancer [JCOG0506 (17)], and head and neck cancer [JCOG0706 (20)] and has adopted non-surgical multimodality treatment such as chemoradiation for esophageal and head and neck cancer and endoscopic resection for mucosal gastric cancer [JCOG0607 (19)]. Furthermore, several institutions of GIOSG have started an investigator-initiated registration trial

Table 1. Clinical trials conducted by GIOSG

Organ	Study no.	Phase	Summary	Ref.
Gastric	8501	rII	Comparing FTM and UFTM for advanced gastric cancer	1
Gastric	8804	II	CDDP + 5′DFUR for advanced gastric cancer	2
Gastric	8903	II	EAP for advanced gastric cancer	3
Gastric	9001	II	FP for advanced gastric cancer	4
Gastric	9205	III	Comparing 5-FUci, FP and UFTM for advanced gastric cancer	5
Gastric	9207	II	MTX + 5-FU as the second line chemotherapy for advanced gastric cancer	6
Gastric	9410	II	5′DFUR for elderly patients with advanced gastric cancer	7
Gastric	9603	II	MTX + 5-FU for malignant ascites of gastric cancer	8
Colorectal	9703	II	CPT-11 + continuous infusion of 5-FU for unresectable metastatic colorectal cancer	9
Esophageal	9906	II	Chemoradiation therapy with 5-FU + CDDP for Stage II/III (except T4) esophageal cancer	10
Esophageal	9908-DI	I/II	Chemoradiation therapy with 254-S + 5-FU for locally advanced esophageal cancer	11
Colorectal	9911-DI	II	CPT-11 + MMC as the second-line chemotherapy for unresectable metastatic colorectal cancer	12
Gastric	9912	III	Comparing 5-FUci, CPT-11 + CDDP and S-1 for advanced gastric cancer	13
Gastric	0106	III	Comparing 5-FUci and MTX + 5-FU for patients with severe peritoneal metastasis of gastric cancer	14
Gastric	0109-DI	II	CPT-11 + MMC as the second-line chemotherapy after failure of 5-FU for advanced gastric cancer	15
Colorectal	0208-DI	I/II	Arterial infusion of 5-FU + systemic infusion of CPT-11 for liver metastasis of colorectal cancer	—
Gastric	0407	rII	Comparing best available 5-FU and weekly PTX as the second-line chemotherapy after failure of 5-FU containing regimen for patients with severe peritoneal metastasis of gastric cancer	16
Pancreatic	0506	II	GEM for locally advanced pancreatic cancer	17
Esophageal	0508[a]	II	Endoscopic resection followed by chemoradiation therapy with 5-FU + CDDP for clinically T1N0M0 esophageal cancer	18*
Esophageal	0604[a]	I/II	Chemoradiation therapy with S-1 + CDDP for Stage II/III (except T4) esophageal cancer: investigator-initiated registration trial	—
Gastric	0607[a]	II	Endoscopic submucosal resection for clinically mucosal cancer	19
Head and neck	0706[a]	II	Chemoradiation therapy with S-1 + CDDP for locally advanced head and neck cancer	20

FTM, futrafur plus MMC; UFTM, uracil and futrafur plus MMC; CDDP, cisplatin; 5′DFUR, 5′-deoxy-5-fluorouridine; EAP, etoposide plus adriamycin and cisplatin; FP, 5-fluorouracil plus cisplatin; 5-FU, 5-fluorouracil; MTX, methotrexate; CPT-11, irinotecan; 254-S, nedaplatin; PTX, paclitaxel; GEM, gemcitabine.
[a]Not completed yet.

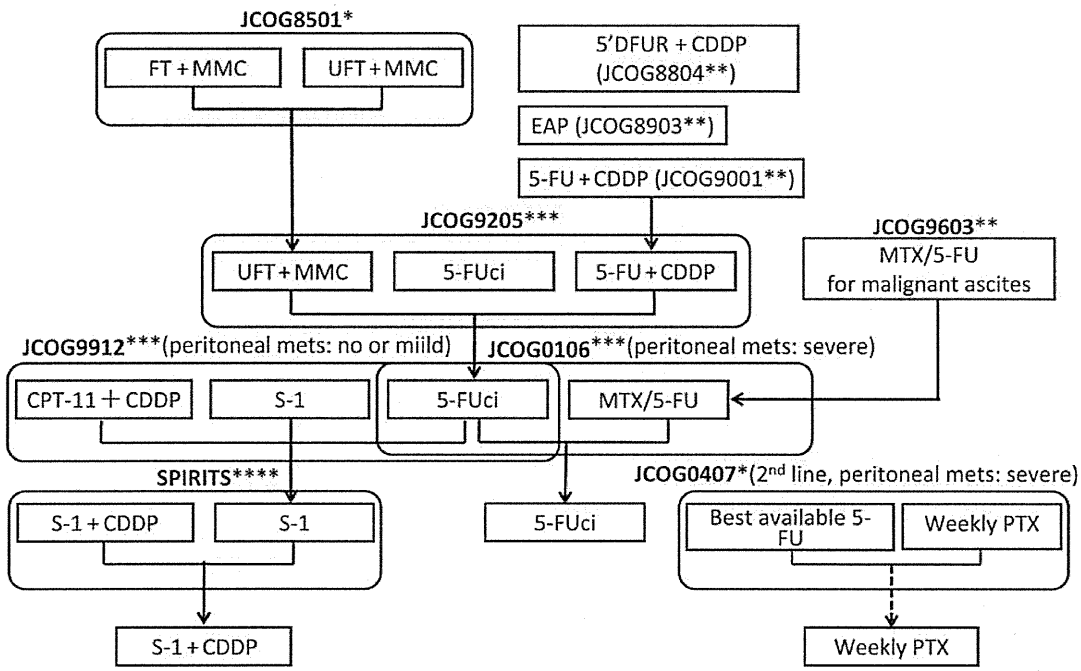

Figure 1. Flow of clinical trials for gastric cancer in GIOSG. Abbreviations are given in the text. *Randomized Phase II, **Phase II, ***Phase III and ****conducted by pharmaceutical company.

(JCOG0604) of S-1 for approval to esophageal cancer. Completion of these clinical trials leads to the establishment of new study groups such as the Hepatobiliary and the Pancreatic Oncology Group, the Gastrointestinal Endoscopy Study Group and the Head and Neck Cancer Study Group in JCOG. GIOSG has merged with Gastric Cancer Study Group as the Stomach Cancer Study Group (SCSG) from 2011. This paper reviews the history of GIOSG, introduces the present activity and proposes the future direction mainly in the field of gastric cancer (Fig. 1).

DAWN OF GIOSG

Till early 1990s, all of GIOSG trials (1–4) were Phase II. In those days, several oral fluoropyrimidines were developed and cisplatin (CDDP) was approved for gastric cancer in Japan. In the randomized Phase II study [JCOG8501 (1)] comparing futrafur plus mitomycin C (MMC) (FTM) with uracil and futrafur plus MMC (UFTM), UFTM showed a higher response rate (25%, $n = 79$) than FTM (8%, $n = 90$). In JCOG8804 (2), 5′-deoxy-5-fluorouridine (5′DFUR) plus CDDP showed a response rate of 50% in 28 patients with measurable lesion. In the Phase II trial [JCOG8903 (3)] of EAP, combination of etoposide, adriamycin (ADM) and CDDP, despite a high response rate and 5-year survival of 10%, treatment-related deaths occurred in 10%. While the dose and schedule of combination of 5-fluorouracil (5-FU) and CDDP (FP) in JCOG9001 (4) were modified from those in Western trials, it showed a response rate (43%, $n = 40$) and survival similar to those of Western trials. From these results, GIOSG concluded that FP and/or UFTM would be selected as test arms for the future Phase III trial.

Table 2. Summary of JCOG9205

Treatment	5-FUci	FP	UFTM
Number of patients	105	105	70
Response rate (%)	11	34	9
Median PFS (days)	58	118	72
Median OS (days)	216	223	176
1-year survival rate (%)	28	29	16
2-year survival rate (%)	7	7	4

PFS, progression free survival; OS, overall survival.

JCOG9205

It was reported that combination chemotherapy consisting of 5-FU, ADM, and MMC did not show a survival advantage over 5-FU alone (25). Consequently, GIOSG conducted a three-arm Phase III [JCOG9205 (5)] trial comparing FP and UFTM with continuous infusion of 5-FU (5-FUci). As a

Table 3. Summary of JCOG9912

Treatment	5-FU	CPT-11 + CDDP	S-1
Number of patients	234	236	234
Response rate (%)	9	38	28
Median PFS (months)	2.9	4.8	4.2
Median TTF (months)	2.3	3.7	4.0
Median OS (months)	10.8	12.3	11.4

TTF, time to treatment failure.

result (Table 2), 280 patients were accrued for 4.5 years, and FP did not show significantly longer survival despite its higher response rate and longer progression-free survival, associated with more severe toxicities than 5-FUci. After intensive discussion about which regimen should be adopted for a control arm in the future trial, FP (global standard) or 5-FUci (winner in JCOG9205), it was concluded that 5-FUci would be a reference arm in the next Phase III trial from the point of overall survival (true endpoint of clinical trials).

JCOG9912

In late 1990s, new anti-tumor agents such as S-1, irinotecan (CPT-11), paclitaxel (PTX) and docetaxel (DTX) were developed and approved for gastric cancer in Japan. From the promising results of Phase II trials of CPT-11 plus CDDP (26) and S-1 (27,28), GIOSG planned a three-arm Phase III study [JCOG9912 (13)] to investigate superiority of CPT-11 plus CDDP and non-inferiority of S-1 compared with 5-FUci with the primary endpoint of overall survival. Seven hundred and four patients were accrued for 5 years. Table 3 summarizes the results of efficacy of JCOG9912. At the primary analysis in March 2007, 1 year after last patient accrual, S-1 showed non-inferiority to 5-FUci [hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.68–1.01, $P < 0.001$ for non-inferiority], while CPT-11 plus CDDP could not show a survival benefit over 5-FUci (HR 0.85, 95% CI 0.70–1.04, $P = 0.055$ for non-inferiority). Additional analysis, 2 years after last patient accrual in May 2008, showed that CPT-11 plus CDDP showed an HR of 0.82 (95% CI 0.68–0.99, $P = 0.0194$), while an HR of S-1 was 0.83 (95% CI 0.68–1.00, $P = 0.0233$ for superiority). In conclusion, S-1 should be considered for the standard chemotherapy of advanced gastric cancer. Thus, S-1 can also replace 5-FUci. Based on the results of JCOG9912, SPIRITS (29) trial, conducted by a pharmaceutical company, which compared S-1 plus CDDP with S-1 showed a survival benefit of S-1 plus CDDP over S-1, leading to the establishment of a standard care for advanced gastric cancer in Japan.

From the present point of view, the quality of JCOG9205 was not so good as the recent clinical trials, JCOG9912 and thereafter, lacking in (i) peer review system of protocol drafts, (ii) central monitoring of case report forms by the data center and a trial office, and (iii) feedback to each investigator. The greatest problem was the speed of patient accrual. While 280 patients were enrolled for about 4.5 years (five patients monthly) in JCOG9205, 704 were for about 6 years (10 patients monthly) in JCOG9912. Actually, JCOG9912 was completed without major violation, including only one ineligible case. It can be said that the quality of the clinical trial in GIOSG was surely improved during JCOG9912.

TRANSLATIONAL RESEARCH

Personalized medicine is one of most important treatment strategies for advanced gastric cancer patients treated with not only molecular target agents but cytotoxic agents because gastric cancer shows very heterogeneous behaviors. GIOSG challenged to a translational research to find predictive marker for chemotherapy effects using the archived tissues of the patients enrolled to JCOG9001 (21), 9205 (22) and 9912 (23,24). The methods of evaluating chemosensitivity-related factors were initially limited to immunohistochemistry using formalin-fixed samples in JCOG9001 and 9205, and recently have progressed to laser-captured microdissection and real-time RT–PCR in JCOG9912. The explorative study along with a Phase II trial of FP (JCOG9001) showed that the number of favorable phenotypes out of five chemosensitivity factors, p53(−), bcl-2(−), vascular endothelial growth factor (VEGF)(+), glutathione *S*-transferase p(−) and thymidylate synthase(−), was a prognostic factor (21), and this result was recapitulated in the confirmative translational study of JCOG 9912 in which pretreatment biopsy were available in 131 of 210 (62%) patients allocated to 5-FUci or FP in the JCOG9205 trial (22). And it was also shown that FP showed a longer survival than 5-FUci among the VEGF(+) patients, while there was no difference in overall survival between the two arms among the VEGF(−) patients. These results suggested that multiple factors may be implicated to chemosensitivity and personalized medicine should be investigated in randomized trials. Then, pretreatment tumor tissue was available from 365 of 704 (52%) patients enrolled in JCOG9912 trial. It was suggested that dihydropyrimidine dehydrogenase might be a selective marker between CPT-11 plus CDDP and S-1 (23) and excision repair cross-complementing group 1 may be an independent prognostic factor for overall survival after first-line treatment of advanced gastric cancer (24).

COMBINED ANALYSIS OF JCOG9205 AND 9912

While both JCOG9205 (5) and 9912 (13) trials contained 5-FUci as control arms, their median overall survivals were 7.1 months in JCOG9205 and 10.8 months in JCOG9912. While about half of the patients received the second-line

chemotherapy in JCOG9205, more than 70% of the patients did in JCOG9912. It is speculated that the second-line chemotherapy might contribute to prolongation of advanced gastric cancer patients. After harmonizing the inclusion criteria of both trials and adjusting patient backgrounds, while time to treatment failure was almost similar (hard ratio, 0.95), overall survival (OS) and survival after treatment failure (OS-TTF) were better in JCOG9912 than JCOG9205 (HR; OS 0.71, 95% CI 0.56–0.99, OS-TTF 0.72, 95% CI 0.57–1.01) (30). Although survival benefit of the second-line chemotherapy for advanced gastric cancer has not been confirmed by randomized Phase III trials, these results suggest that the second-line chemotherapy with new agents approved in late 1990s such as CPT-11, PTX, and DTX might have contributed to the prolongation of the OS because there were no active drug for the second-line chemotherapy in the era of JCOG9205.

JCOG0106 AND 0407

Peritoneum is one of the common metastatic sites as well as liver and lymph nodes. The incidence of peritoneal metastasis is higher than 50% among patients with advanced gastric cancer. The prognosis of patients with severe peritoneal metastasis is considered to be poor because it causes various complications such as ascites, bowel obstruction and hydronephrosis, and deteriorates patient's general condition. Moreover, these patients usually do not have target lesions according to RECIST. For these reasons, patients with severe peritoneal metastasis are usually excluded from clinical trials. Thus, evidence from clinical trials can hardly be applied to these patients and the standard chemotherapy for them has not been established.

GIOSG challenged to the Phase III trial [JCOG0106 (14)] targeting to the patients with severe peritoneal metastasis, comparing sequential therapy of 5-FU and methotrexate (MTX) (MF) based on the results of JCOG9603 (8), in which massive ascites remarkably decreased in 13 out of 37 patients (35%) by MF therapy. In JCOG0106, a total of 237 patients were enrolled for 4.5 years, and MF could not show a survival benefit over 5-FUci [median survival time (MST); 5-FUci/MF 9.4/10.6 months, HR 0.94, 95% CI 0.72–1.22, $P = 0.31$].

Although not a few patients are complicated with severe peritoneal metastasis after failure in the first-line chemotherapy, the second-line chemotherapy is limited by patient's poor condition. Thus, GIOSG conducted a randomized Phase II trial [JCOG0407 (16)] comparing best available 5-FU with weekly administration of PTX for the patients with severe peritoneal metastasis in the second-line chemotherapy after failure in the first-line chemotherapy containing fluoropyrimidine. MST in each arm was the same, 7.7 months, and survival at 1 year was 31.4% in weekly PTX and 27.1% in best available 5-FU (HR = 0.887, 95% CI 0.571–1.377, $P = 0.298$), associated with less toxicity of PTX. Thus, JCOG0407 suggested activity and feasibility of weekly PTX for gastric cancer patients with severe peritoneal metastasis in the second line.

AT PRESENT

In 2006, Japanese guideline changed and requires a Phase III trial for approval of new anti-cancer agents. Before JCOG9912, new agents such as CPT-11 and S-1 had been approved only after completing Phase II trials, and JCOG could run a Phase III trial using these new agents to investigate survival benefit of these new drugs. Top 5 of 37 institutions in GIOSG enrolled more than half of the patients of JCOG9912, and top 10 institutions covered two-thirds of all. After JCOG9912, many industry-sponsored registration Phase III trials of new molecular target agents, such as trastuzumab, bevacizumab and cetuximab in the first line and lapatinib and everolimus in the second line, have been conducted globally, and some of top institutions with high activity in GIOSG have participated to them. This means leading institutions of GIOSG have contributed to both JCOG and registration trials. However, it was difficult to participate simultaneously both in JCOG trials and to registration trials, and actually there has been no clinical trial of chemotherapy for advanced gastric cancer since completion of JCOG0407 in 2008.

At present, GIOSG has been planning two Phase III trials. One is a trial of triplet chemotherapy which may cause severe hematological toxicity, investigating additional effects of DTX on S-1 plus CDDP, accompanied by translational research for personalized medicine. The other trial focuses on poor conditioned patients who cannot take even oral drugs or receive large volume hydration due to severe peritoneal metastasis with/without ascites, comparing weekly PTX

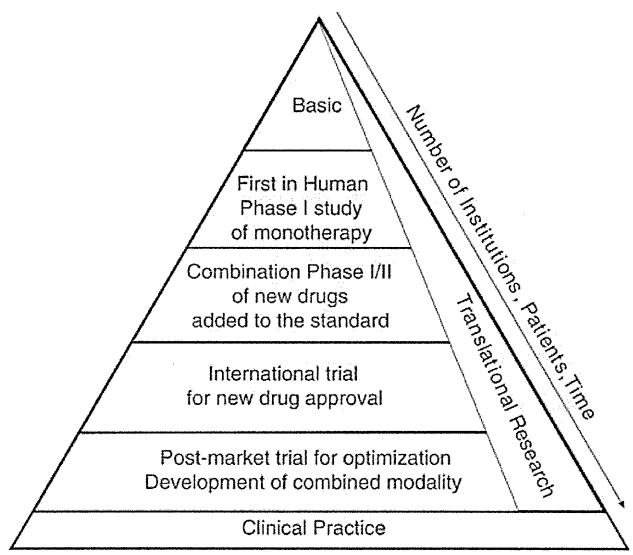

Figure 2. Step and role for progress in new drug development.

plus 5-FU/leucovorin with 5-FU/leucovorin. It is planned that this study will be conducted in collaboration with WJOG. GIOSG have merged with Gastric Cancer Study Group as the SCSG from 2011. It is expected that the activity of SCSG will be increased by synergistic effects of collaboration between medical oncologists and surgeons.

FUTURE DIRECTION

It is well known that many steps from basic reach to Phase III trial for new drug approval. Furthermore, optimization of new drug is necessary to obtain better outcome in clinical practice such as multimodality treatment, treatment strategy covering all through clinical course and personalized medicine. All these steps are very important for progress in cancer treatment (Fig. 2). From the point of the roles shared with many other clinical trial groups, and pharmaceutical companies which are the main promoters of new drugs development, SCSG should recognize its own role. It is considered that the most important role of SCSG is to conduct a post-market trial for establishing new standard treatment in clinical practice, containing multimodality treatments, translational research, second-line chemotherapy and personalized medicine. Especially, because the recent indication of new drugs has been limited for 'unresectable or recurrent disease' and not for perioperative setting of resectable disease, SCSG consisting of both medical oncologist and surgeons should collaborate to conduct an investigator-initiated Phase III trial for expanding the indication of new drugs to perioperative chemotherapy (e.g. herceptin in the adjuvant setting for Her-2-positive gastric cancer) in the near future. Finally, the future trials should be large scale and focus on optimization of new drugs in multimodality treatments. Thus, collaboration with the other clinical trial groups, pharmaceutical companies and government, not only in Japan but in the global, will be dispensable. In conclusion, SCSG should make efforts to conduct clinical trials with high quality for new standard treatment.

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Conflict of interest statement

None declared.

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PHASE II STUDIES

Phase II study of sunitinib as second-line treatment for advanced gastric cancer

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Summary *Purpose.* This phase II, open-label, multicenter study assessed the oral, multitargeted, tyrosine kinase inhibitor sunitinib in patients with advanced gastric or gastroesophageal junction adenocarcinoma who had received prior chemotherapy. *Experimental design.* Patients received sunitinib 50 mg/day on Schedule 4/2 (4 weeks on treatment, followed by 2 weeks off treatment). The primary endpoint was objective response rate; secondary endpoints included clinical benefit rate, duration of response, progression-free survival (PFS), overall survival (OS), pharmacokinetics, pharmacodynamics, safety and tolerability, and quality of life. *Results.* Of 78 patients enrolled,

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most had gastric adenocarcinoma (93.6%) and metastatic disease (93.6%). All were evaluable for safety and efficacy. Two patients (2.6%) had partial responses and 25 patients (32.1%) had a best response of stable disease for ≥6 weeks. Median PFS was 2.3 months (95% confidence interval [CI], 1.6–2.6 months) and median OS was 6.8 months (95% CI, 4.4–9.6 months). Grade ≥3 thrombocytopenia and neutropenia were reported in 34.6% and 29.4% of patients, respectively, and the most common non-hematologic adverse events were fatigue, anorexia, nausea, diarrhea, and stomatitis. Pharmacokinetics of sunitinib and its active metabolite were consistent with previous reports. There were no marked associations between baseline soluble protein levels, or changes from baseline, and measures of clinical outcome. *Conclusions*. The progression-delaying effect and manageable toxicity observed with sunitinib in this study suggest that although single-agent sunitinib has insufficient clinical value as second-line treatment for advanced gastric cancer, its role in combination with chemotherapy merits further study.

Keywords Sunitinib · Gastric cancer · Tyrosine kinase inhibitor · Pharmacokinetics · Pharmacodynamics

Introduction

Gastric cancer is the fourth most common cancer globally, with an estimated 934,000 new cases in 2002 [1]. Patients presenting or relapsing with metastatic disease have a poor prognosis, and with 700,000 deaths annually, gastric cancer is the second most common cause of death from cancer worldwide [1]. In Japan and Korea, mass screening has led to a shift towards diagnosis at earlier stages of the disease, and the 5-year survival rate is relatively high at 40–60% [2, 3]. Globally, 5-year survival is lower, at approximately 20% [2]. In clinical trial patients with advanced gastric cancer, reported median survival commonly ranges from 8 months to 11 months in the first-line treatment setting and approximately 5 months to 6 months in the second-line treatment setting [4–6].

Combination chemotherapy prolongs survival and improves quality of life in patients with gastric cancer, compared with best supportive care [7, 8]. Recently, a meta-analysis showed a small but significant survival benefit for combination chemotherapy versus single-agent chemotherapy, though at a cost of higher toxicity [8]. There is no globally accepted standard regimen for first-line treatment of advanced gastric cancer, though a 5-fluorouracil-based regimen in combination with a platinum analog is reported to be the most widely accepted regimen [9]. As yet, there are no data showing acceptable efficacy for gastric cancer in the second line setting. New treatment strategies are still needed to improve the survival of patients with advanced gastric cancer, both in the first-line treatment setting and in those patients whose disease has progressed during or after chemotherapy.

Tumor angiogenesis, growth, and metastasis can be inhibited by blocking receptor tyrosine kinases (RTKs), including vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs), which are both expressed or overexpressed in gastric cancer [10–12]. VEGF and PDGF-A expression have been linked to tumor progression and poor survival in gastric cancer [13, 14], and both VEGF and VEGFR expression have been correlated with increasing stage of disease [15]. Treatments that specifically interrupt RTK signalling pathways have been investigated in phase II studies in advanced gastric cancer, including a study of single-agent gefitinib [16, 17] and targeted therapies such as bevacizumab [18], cetuximab [19, 20], and erlotinib [21] in combination with chemotherapy. These targeted agents act through a single receptor pathway. However, many gastric tumors co-express several RTKs [10] and drugs targeting multiple RTKs involved in angiogenesis may deliver additional benefits relative to single receptor target inhibition.

Sunitinib malate (SUTENT®; Pfizer Inc., New York, NY) is an oral, multitargeted tyrosine kinase inhibitor of VEGFR-1, -2, and -3, PDGFR-α and -β, and several other related RTKs [22–24]. In a murine xenograft model of gastric carcinoma, sunitinib exhibited antiangiogenic and antitumor activity at a dose of 40 mg/kg/day (Pfizer Inc. Data on file). At a dose of 50 mg/day given on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment), sunitinib has demonstrated superior efficacy to previous standard treatments and acceptable tolerability in gastrointestinal stromal tumors refractory or intolerant to imatinib, and advanced renal cell carcinoma [25, 26]. This phase II trial investigated the use of single-agent sunitinib in patients with previously-treated, advanced gastric carcinoma.

Materials and methods

Patients

Patients eligible for inclusion were males and females aged ≥18 years with histologically or cytologically confirmed

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diagnosis of gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (i.e. adenocarcinoma with >50% extension in the stomach) that was not amenable to surgery, radiation, or combined modality therapy with curative intent, and who had disease progression or recurrence after treatment with one prior chemotherapy regimen for advanced or metastatic disease (last dose ≥4 weeks before study entry).

Patients who had received prior adjuvant therapy were eligible if relapse occurred >6 months after completing adjuvant treatment and had received one regimen for relapsed disease. Those who had received prior palliative radiotherapy to metastatic lesions were also eligible, if at least one measurable lesion had not been irradiated. Patients were excluded if they had: major surgery or radiation therapy <4 weeks before starting study treatment; grade 3 hemorrhage (based on the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) <4 weeks before starting study treatment; presence of clinically relevant ascites (requiring paracentesis) and/or grade ≥2 weight loss; active inflammatory bowel disease, partial or complete bowel obstruction, or chronic diarrhea; known brain metastases, spinal cord compression, or carcinomatous meningitis; uncontrolled hypertension; clinically significant cardiovascular disease (severe/unstable angina, myocardial infarction, coronary artery bypass graft, symptomatic congestive heart failure), pulmonary embolism, or cerebrovascular accident within 12 months prior to study drug administration; ongoing cardiac dysrhythmias (NCI CTCAE grade ≥2), atrial fibrillation, or prolongation of the QTc interval; or any other severe acute or chronic medical or psychiatric condition making the patient inappropriate for entry into the study in the judgment of the investigator.

All patients had: measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST); Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1; adequate hepatic, renal, and hematologic function; and life expectancy of ≥3 months; and were required to provide written, informed consent.

Study design and treatment

In this phase II, open-label, 2-stage, multicenter study, patients received oral sunitinib 50 mg/day on Schedule 4/2 (4 weeks on treatment, followed by 2 weeks off treatment) in repeated 6-week cycles, until disease progression, unacceptable toxicity, or withdrawal of consent. Dose reduction to 37.5 mg/day and then to 25 mg/day was allowed, and therapy could be interrupted or delayed for up to 4 weeks according to individual tolerability.

The primary objective of this study was to determine the antitumor activity of single-agent sunitinib in this population. The primary endpoint was the overall objective response rate (ORR), defined as the percentage of all patients who experienced a confirmed complete response (CR) or partial response (PR), as defined by RECIST [27]. Secondary endpoints included duration of response (in those with an objective response of CR or PR); clinical benefit rate (CBR, defined as the percentage of patients with CR, PR, or stable disease [SD] ≥24 weeks); progression-free survival (PFS); time to progression (TTP); OS; one-year survival rate; safety and tolerability; health-related quality of life (HRQoL); and measurement of trough sunitinib and SU12662 (the major active metabolite of sunitinib) plasma levels, as well as levels of plasma biomarkers (VEGF, soluble (s) VEGFR2, sVEGFR3, and sKIT). This study was approved by the institutional review board of each participating center and was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, as well as applicable local laws and regulatory requirements.

Assessments

Tumor response was assessed according to RECIST version 1.0, with a minor modification such that lesions assessed using spiral computed tomography (CT) scan qualified as measurable if they were twice the reconstruction interval used (up to 8 mm) and at least 10 mm at baseline. Tumor response was assessed: on day 28 of every cycle; whenever disease progression was suspected; to confirm a CR or PR (at least 4 weeks after initial documentation of response); and at the end of study treatment or withdrawal from the study. Tumors were imaged using CT scan or magnetic resonance imaging.

Safety was assessed at regular intervals by monitoring and recording adverse events and by measuring hematology and clinical chemistries. Additional safety assessments included 12-lead electrocardiograms, vital signs, physical examination, and ECOG performance status. Adverse events were graded using NCI CTCAE, version 3.0.

Blood samples were taken for pharmacokinetic analysis of sunitinib and SU12662 prior to sunitinib treatment on study day 1, on days 14 and 28 of the first treatment cycle, on days 1 and 28 of cycles 2 and 3, and on day 28 of cycle 5. Sunitinib and SU12662 concentrations were analyzed using a validated, sensitive, and specific isocratic liquid chromatographic tandem mass spectrometric method, as previously described [28]. Blood samples for biomarker assessment were taken prior to sunitinib treatment on study day 1, on days 14 and 28 of the first treatment cycle, on days 1 and 28 of cycle 2, and on day 28 of cycle 5.

Patient-reported outcomes were assessed using the validated, self-administered European Organisation for Research and Treatment of Cancer (EORTC) Quality of

Life Questionnaire QLQ-C30, and the stomach cancer-specific questionnaire QLQ-STO22 [29, 30]. The questionnaires were completed on the first day of each cycle during a patient's clinic visit prior to other clinical activities including the administration of the study drugs, and at the end of treatment or withdrawal from the study.

Statistical considerations

This study followed a 2-stage Simon design. If ≤1 objective response (CR or PR) was observed in the first 38 eligible patients, then enrollment to the study would end. If ≥2 of these patients achieved a CR or PR, then the study was planned to proceed to Stage 2 by enrolling 25 additional patients. Based on Simon's 2-stage design, this study had 85% power to reject the null hypothesis of a 5% response rate (considered not clinically meaningful) when the true response rate for sunitinib was ≥15% (considered favorable in this patient population). With a significance level (α) of 5%, 63 eligible patients were required, and at the end of the study, the null hypothesis would be rejected if ≥7 objective tumor responses were observed.

The study population for all analyses was defined as the number of patients enrolled in the study who received at least one dose of sunitinib, and (for analysis of ORR, duration of response, CBR, TTP, and PFS) had measurable disease at baseline. The number (%) of patients who achieved an objective response was summarized along with the corresponding 95% exact confidence interval (CI). Time-to-event variables, 1-year survival rate, and a 2-sided 95% CI were estimated and summarized using the Kaplan-Meier method.

Results

Patient characteristics and study treatment

In total, 78 patients were enrolled in the study (Fig. 1), of whom 73 (93.6%) had a diagnosis of gastric adenocarcinoma, and 5 (6.4%) had adenocarcinoma of the gastroesophageal junction. A total of 73 patients (93.6%) had metastatic disease. Baseline characteristics are summarized in Table 1.

The median duration of treatment was 1.6 months (range, 0.1–15.4), and the median number of cycles started was 2 (range, 1–17). Fourteen patients (17.9%) required at least one dose reduction to 37.5 mg/day, mainly due to hematologic adverse events; three of these patients had ≥2 dose reductions. Median relative dose intensity was 93.5%. The relative dose intensity was highest during cycles 1 and 2 (96.4% and 100%, respectively) and ranged from 50.0% to 96.4% during cycles 3–17. Sixteen patients (20.5%) required one or more doses of sunitinib to be delayed, with 12 dose delays lasting for ≥1 week, 6 for ≥2 weeks, and 1 for ≥3 weeks. Reasons for study discontinuation were lack of efficacy (n=55), adverse events (n=11), death (n=8), and withdrawal of consent (n=2).

During follow-up, among 69 patients for whom data were available, 39 received post-study chemotherapy; the most common regimens were single-agent taxanes, FOLFIRI or FOLFOX, or cisplatin-based combinations. Japanese and Korean patients were most likely to receive later lines of chemotherapy (approximately 75% of enrolled patients) but no significant differences were noted in the types of chemotherapy delivered. Five patients received radiotherapy during the follow-up period, and one underwent surgical resection of metastatic ovarian cancer.

Efficacy

All 78 patients had measurable disease at baseline and were included in the efficacy analyses. Two patients achieved confirmed investigator-determined PR, with a response duration of 20 weeks in one patient and at least 6 weeks (before study discontinuation) in the other patient. Both patients achieving a PR were enrolled in Stage 1 of the study, hence the study proceeded to Stage 2. However, with no further responses seen during Stage 2, the primary endpoint of the study was not met, with an ORR of 2.6%. Twenty-five patients (32.1%) had stable disease (SD) for ≥6 weeks, including four patients (5.1%) experiencing SD lasting ≥24 weeks. The clinical benefit rate was 7.7%.

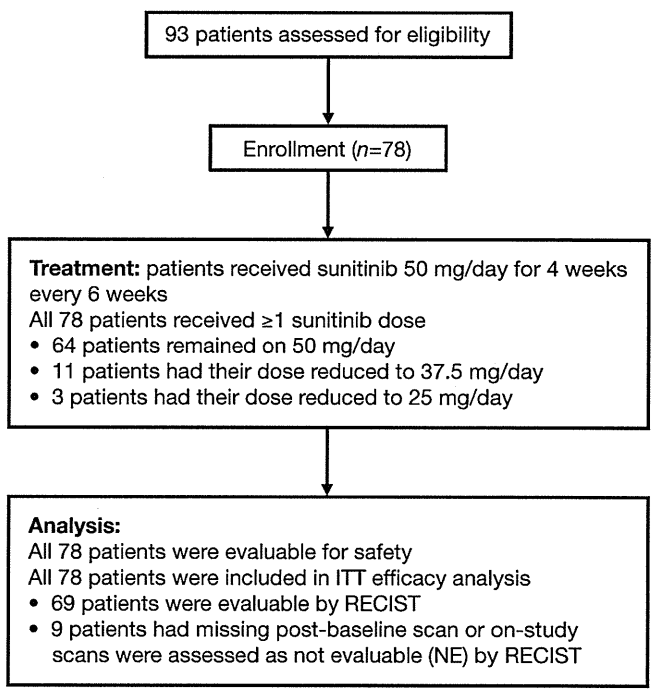

Fig. 1 Patient disposition. ITT, intention-to-treat. RECIST, Response Evaluation Criteria in Solid Tumors

Table 1 Patient baseline characteristics

	Patients receiving sunitinib (N=78)
Median age (range), years	56 (25–78)
Gender (male/female), *n* (%)	56 (71.8) / 22 (28.2)
ECOG PS, *n* (%)	
0	26 (33.3)
1	52 (66.7)
Histopathology, *n* (%)	
Gastric adenocarcinoma	73 (93.6)
Gastroesophageal junction adenocarcinoma	5 (6.4)
Histological grade, *n* (%)	
Well differentiated	9 (11.5)
Moderately differentiated	26 (33.3)
Poorly differentiated	35 (44.9)
Undifferentiated	3 (3.8)
Cannot be assessed	5 (6.4)
Extent of disease, *n* (%)	
Locally advanced	5 (6.4)
Metastatic	73 (93.6)
Prior treatment, *n* (%)	
Chemotherapy	78 (100.0)
Radiation therapy	6 (7.7)
Surgery	59 (75.6)

ECOG PS Eastern Co-operative Oncology Group performance status

Forty-two patients (53.8%) experienced disease progression; the remaining nine patients (11.5%) had missing evaluations or were not evaluable.

By intent-to-treat analysis (n=78), median TTP was 2.3 months (95% CI, 1.7–2.6 months), median PFS was 2.3 months (95% CI, 1.6–2.6 months; Fig. 2a), and median OS was 6.8 months (95% CI, 4.4–9.7 months; Fig. 2b). The probability of 1-year survival was 24.2% (95% CI, 14.4–34.1%).

Pharmacokinetics and pharmacodynamics

Steady-state observed trough concentrations (C_{trough}) were dose-corrected to the starting dose (i.e. reference dose) where appropriate, to adjust for individual dose changes during the study. Mean, dose-corrected, plasma C_{trough} on day 28 (steady state) of cycles 1, 2, 3, and 5 ranged from 62.2 ng/mL to 65.6 ng/mL for sunitinib, 26.0 ng/mL to 33.7 ng/mL for its active metabolite SU12662, and 90.7 ng/mL to 97.9 ng/mL for total drug (sunitinib + SU12662), respectively. The mean dose-corrected C_{trough} box plot of the total drug concentration versus cycle/day is displayed in Fig. 3. No unexpected accumulation of sunitinib and SU12662 was observed throughout the study.

Baseline soluble protein (biomarker) levels or changes from baseline at each time point were analyzed in patients stratified by tumor response category (clinical benefit [PR

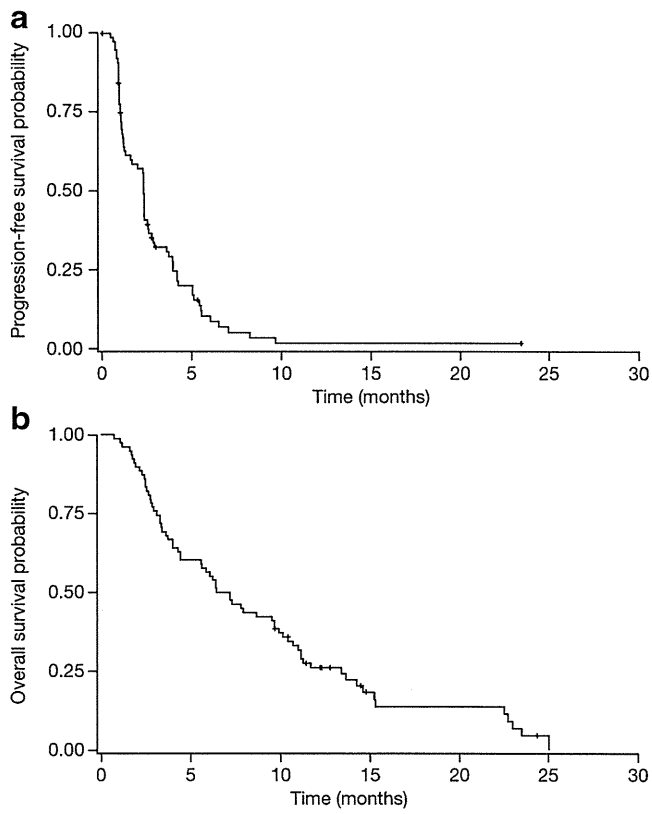

Fig. 2 Kaplan-Meier curve of a progression-free survival and **b** overall survival following treatment with sunitinib 50 mg/day on Schedule 4/2

or SD ≥24 weeks] versus progressive disease). Significant associations with clinical benefit were only observed between high sKIT ratio to baseline at cycle 1 day 28 (P=0.0081), and between low VEGF-C ratio at cycle 2 day 1 (P=0.0326), though the number of patients with clinical benefit was relatively small (n=6). Analysis of patients stratified according to whether they were above or below median time-to-event endpoints for PFS or TTP found no significant differences in any of the soluble proteins studied; there was a modest association between elevated baseline plasma VEGF-C levels and above-median OS (P=0.0241).

Safety

All 78 patients received at least one dose of sunitinib and were included in the safety analyses (Table 2). The most commonly reported treatment-emergent, all-causality, non-hematologic adverse events were fatigue, anorexia, nausea, diarrhea, and stomatitis (Table 2). Most non-hematologic adverse events were grade 1 or 2. Grade 3 or 4 events included fatigue (10.3%), anorexia, hand–foot syndrome, hyperbilirubinemia (6.4% each), and abdominal pain (5.1%). The most common hematologic toxicities were thrombocytopenia (61.5% of patients; 34.6% grade 3 or 4, and one patient with a grade 5 event) and neutropenia (52.6% of patients, 29.4% grade 3 or 4). Thirteen patients (16.7%) experienced grade 3 or 4 anemia. There were no cases of neutropenic fever. Of non-hematologic laboratory adverse events, blood alkaline phosphatase was increased in 10.3% of the study population and occurred at grade 3, the maximum grade reported, in only two patients. Increases in gamma glutamyl transferase were infrequent (2.6%) and of grade 2 severity.

Twenty-four patients (30.8%) permanently discontinued study treatment due to an adverse event; in 14 patients, the adverse events were judged by the investigators to be treatment related. Non-fatal, treatment-related adverse events leading to discontinuation were grade 3 fatigue (n=2) and grades 2 and 4 mucositis, grade 3 nausea, grade 1 ascites, grade 4 thrombocytopenia, grade 3 hand–foot syndrome, grade 4 abdominal pain plus grade 1 anorexia, and combined grade 2 thrombocytopenia and grade 1 nausea, stomatitis, fatigue, skin erosion and hand–foot syndrome (n=1 each). Non-treatment-related discontinuations due to adverse events were attributed by investigators to the disease under study (n=8) or other illness (n=2; stomach cancer perforation and infection, respectively).

Table 2 Treatment-emergent, all-causality adverse events (any cycle) reported in ≥15% of patients

	Number of patients (%) (N=78)	
	All-grade	Grades 3/4
Non-hematologic		
Fatigue	35 (44.9)	8 (10.3)
Anorexia	35 (44.9)	5 (6.4)
Nausea	32 (41.0)	3 (3.8)
Diarrhea	28 (35.9)	2 (2.6)
Stomatitis	28 (35.9)	1 (1.3)
Vomiting	24 (30.8)	3 (3.8)
Hand–foot syndrome	22 (28.2)	5 (6.4)
Pyrexia	22 (28.2)	
Abdominal pain	20 (25.6)	4 (5.1)
Skin discoloration	19 (24.4)	
Constipation	17 (21.8)	1 (1.3)
Hypoalbuminemia	15 (19.2)	
Rash	14 (17.9)	
Mucosal inflammation	13 (16.7)	2 (2.6)
Hyperbilirubinemia	13 (16.7)	5 (6.4)
Hematologic		
Thrombocytopenia	48 (61.5)[a]	27 (34.6)
Neutropenia	41 (52.6)	23 (29.4)
Leukopenia	30 (38.5)	9 (11.5)
Anemia	29 (37.2)	13 (16.7)

[a] Includes one grade 5 event

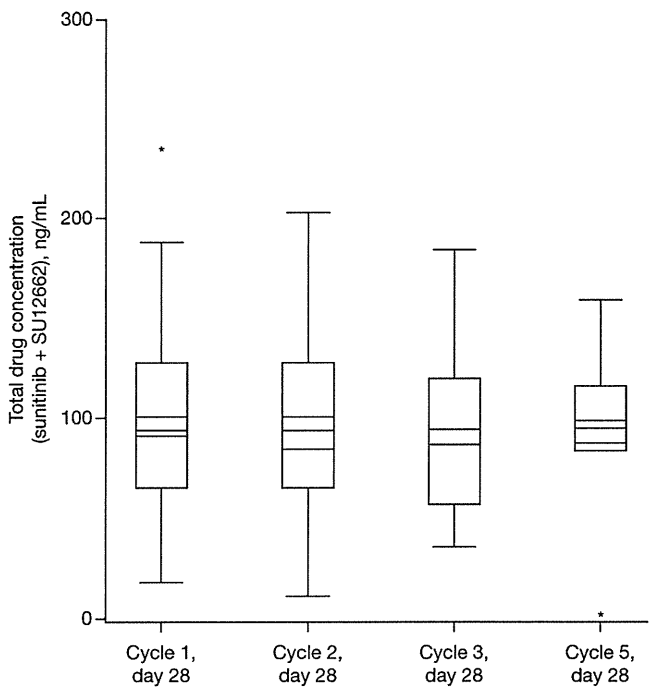

Fig. 3 Total drug (sunitinib + SU12662) dose-corrected (reference dose: 50 mg) plasma trough concentration versus cycle/day box plot. Box boundaries denote 25th and 75th percentiles; lines within the box show the median value and expected range of the median. Whiskers indicate the minimum and maximum data values; where outliers are present (asterisks), whiskers extend to a maximum of 1.5 times the interquartile range

Nine patients (11.5%) had a dose reduction due to treatment-emergent adverse events, all of which were treatment-related.

Eleven patients (14.1%) died during the reporting period (during treatment or within 28 days after the last dose of study drug), with eight of these patients having death as the reason for discontinuation of the study. Four of the 11 deaths were considered to be treatment-related adverse events (three during treatment and one within 28 days after the last dose of sunitinib) and seven due to adverse events unrelated to treatment (six due to disease progression; one due to hypotension, depressed level of consciousness and hypopnea). The deaths considered to be treatment-related were due to thrombocytopenia and pulmonary embolism; brain herniation (preceded by upper gastrointestinal bleeding at day 14); cardiac arrest; and brainstem hemorrhage occurring 21 days after the last dose of study drug, respectively.

HRQoL

QLQ-C30 questionnaires were completed by 64 patients at baseline (cycle 1, day 1); completion rates were generally high during treatment but upon withdrawal from the study the completion rate fell to 69.2%. From a mean baseline global health status/HRQoL of 62.3, HRQoL was maintained by sunitinib treatment during the first three cycles of this study, though the domains of diarrhea and reflux symptoms were noticeably worse compared to baseline. Beyond cycle 3, HRQoL data were available for <10 patients per cycle due to study discontinuations.

At patients' last evaluation (end of treatment or withdrawal from the study), noticeable changes (deterioration) were observed in most scales and measures of the EORTC QLQ-C30 and QLQ-STO22 compared to the baseline. The domains for perceived financial difficulties, body image, and hair loss did not change noticeably.

Discussion

In this study, sunitinib showed preliminary activity in the second-line treatment setting in patients with advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma. Following two objective responses in Stage 1, both stages of the study were enrolled, but overall the study did not meet its primary endpoint, with only two patients achieving a PR by RECIST for an overall RECIST-defined ORR of 2.6%. However, the clinical benefit rate was 7.7% and one-third of patients experienced a best response of SD. The median OS duration of 6.8 months, and the median PFS and TTP of 2.3 months with single-agent sunitinib in this study are comparable with those reported in the second-line treatment setting in similar phase II trials of single-agent chemotherapy, such as docetaxel [31, 32], paclitaxel [33, 34], irinotecan [35], or mitomycin C [36], as well as various chemotherapy combinations [4–6]. This level of efficacy is clearly insufficient to support further study of sunitinib as a single-agent in this population, although these data support the proof of concept that sunitinib does affect the late clinical course of gastric cancer.

Recently, the use of trastuzumab in combination with chemotherapy was found to significantly prolong survival when given as first-line treatment for patients with HER2-positive gastric or gastroesophageal cancer [37]—this is the first time that a regimen including a targeted agent has been shown to provide a survival benefit in patients with advanced gastric cancer. It can be hypothesized that the progression-delaying effects observed with sunitinib in our trial might be enhanced if sunitinib is given in combination with chemotherapy, and this is being investigated in the first-line treatment setting in phase I trials at present.

In general, the type and frequency of reported adverse events were consistent with those previously reported with sunitinib when administered as a single agent [25, 26, 38, 39]. Adverse events were generally manageable, as dose schedule modifications (mainly dosing delays) were required in less than half of the patients, though the incidence of permanent discontinuations due to treatment-related adverse events was 18%. This included four (5.1%) treatment-related deaths (thrombocytopenia/pulmonary embolism, brain herniation preceded by upper gastrointestinal bleeding, cardiac arrest, and one patient who died 21 days after the last dose of study drug from brainstem hemorrhage). The predominant non-fatal, treatment-related adverse events leading to discontinuation were fatigue and mucositis. Most non-hematologic adverse events were Grade 1 or 2 in severity. The most common Grade 3 or 4 non-hematologic events included fatigue, anorexia, hand–foot syndrome, hyperbilirubinemia, and abdominal pain, each reported in ≤10% of patients. However, the incidence and severity of hematologic adverse events during sunitinib treatment was higher in this population than in gastrointestinal stromal tumor (GIST) and metastatic renal cell carcinoma (mRCC) patients [25, 26]. Grade 3 or 4 neutropenia or thrombocytopenia was reported in approximately one-third of patients, but only one case of hemorrhagic thrombocytopenia was reported, and there were no cases of neutropenic fever. The majority of adverse events were managed by standard medical intervention and sunitinib dosing interruption, with or without dose reduction.

Analysis of the HRQoL endpoints measuring gastric cancer-related symptoms, general cancer-related symptoms, overall health status and quality of life shows that these scores were largely maintained during the first three cycles