low grade MALT with diffuse large component have not shown any different behavior from those without diffuse large component. In the Japanese studies, some patients resistant to those non-surgical treatments underwent salvage surgery without significant morbidity even in cases after radiation therapy. These results support the optimal treatment series for low grade MALT lymphoma: primarily eradication, second line radiation therapy to eradication-resistant tumors, and salvage surgery if these conservative treatments fail.

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Long-term Survival and Prognostic Factors in Patients with Metastatic Gastric Cancers Treated with Chemotherapy in the Japan Clinical Oncology Group (JCOG) Study

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Background: The long-term survival of patients after chemotherapy for advanced gastric cancer remains unclear. The aim of this analysis was to investigate prognostic factors for patients with metastatic gastric cancer treated by chemotherapy, and to identify the characteristics of long-term survivors.

Methods: Six hundred and forty three patients were enrolled in four phase II studies and one phase III study by the Japan Clinical Oncology Group between January 1985 and April 1997. By adjusting patients' eligibility between the five studies, 497 patients (77%) were selected for the analysis. Univariate and multivariate analyses were performed using log-rank tests and Cox's proportional hazard model, respectively.

Results: Of the 497 patients analyzed, 39 (8%) and 11 (2%) patients have survived longer than 2 and 5 years, respectively. By multivariate analysis, better performance status, a small number of metastatic sites and macroscopically non-scirrhous type tumors were significantly associated with better prognosis. Characteristics of the 11 5-year survivors revealed eight with para-aortic node metastases alone. Eight of these patients received gastrectomy; four underwent it before chemotherapy, and the other four patients received it after achieving downstaging with successful chemotherapy.

Conclusions: These results demonstrated that better performance status, a small number of metastatic sites and macroscopically non-scirrhous type tumors are independent favorable factors for survival. There were a few 5-year survivors with unresectable gastric cancers, most of whom had only abdominal lymph node metastases and received gastrectomy before or after chemotherapy.

Key words: gastric cancer – chemotherapy – long-term survival – prognostic factors

INTRODUCTION

Gastric cancer remains one of the major leading causes of death worldwide. For unresectable advanced or recurrent gastric cancers, systemic chemotherapy has marginal survival benefits as compared with best supportive care (1–4), though it has only palliative impact. Over the past 20 years, many chemotherapeutic agents—often as combination regimens—have been studied in gastric cancer. Although there have been some recent reports of very high response rates with the newer combination regimens, no standard regimens have been established, and the median survival time of patients with advanced gastric cancer still remains <1 year. In each of the phase II and phase III studies, outcomes have usually been evaluated as median survival times and 1- or 2-year survival rates. However, there have been few multivariate analyses based on a sufficient number of patients to evaluate the impact of chemotherapy, when combined with prognostic factors, on long-term survival of patients with metastatic gastric cancers.

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Between 1985 and 1997, the Japan Clinical Oncology Group (JCOG) carried out one randomized phase II study, three series of phase II studies and one randomized phase III study, for ~600 patients with unresectable gastric cancer (5–9). Although some combination regimens have been attempted in our group, no regimens have demonstrated survivals significantly superior to those with the single agent 5-fluorouracil (5-FU). Before initiating the last phase III study, we reported (10) the preliminary long-term results of the 226 patients enrolled, which revealed 2- and 5-year survivals of 10 and 4%, respectively. However, the number of patients in that analysis was too small to clarify long-term survival and to carry out multivariate analysis for prognosis. We have now re-analyzed the long-term survivals using multivariate analysis, after obtaining long-term outcomes with a minimum follow-up period of 5 years for patients registered in the large multi-institutional phase III study. The aim of this analysis was to clarify the impact of chemotherapy on long-term results and prognostic factors in patients with unresectable advanced and recurrent gastric cancers.

PATIENTS AND METHODS

PATIENT SELECTION

Between January 1985 and April 1997, 643 patients were enrolled in four phase II and one phase III JCOG study (study numbers 8501, 8804, 8903, 9001 and 9205, listed in Table 1). The chemotherapy consisted of the following six regimens: (i) tegafur 500 mg/m^2 per day on days 1–28 + mitomycin C 5 mg/m^2 per day on days 1, 8, 15 and 22 every 4 weeks (FTM); (ii) uracil-tegafur 375 mg/m^2 per day on days 1–28 + mitomycin C 5 mg/m^2 per day, on days 1, 8, 15 and 22 every 4 weeks (UFTM); (iii) 5′-doxifluridine 1400 mg/m^2 per day on days 1–4 and 15–18 + cisplatin 80 mg/m^2 per day on day 5, every 4 weeks (5′P); (iv) etoposide 100 mg/m^2 per day on days 4–6 + doxorubicin 20 mg/m^2 per day on days 1 and 7 + cisplatin 40 mg/m^2 per day on days 2 and 8, every 4 weeks (EAP); (v) 5-FU 800 mg/m^2 per day on days 1–5 + cisplatin 20 mg/m^2 per day on days 1–5, every 4 weeks (FP); and (vi) continuous infusion of 5-FU 800 mg/m^2 per day on days 1–5, every 4 weeks (5-FUci). In the earlier studies (8501 and 8804), patients with potentially resectable cancers were included, because patients whose medical complications made surgical intervention unsuitable were accepted as eligible. To adjust the patients' eligibility between the five studies, 497 (77%) patients who met the following criteria were selected from the 643 case report forms: (i) histologically proven adenocarcinoma of the stomach with measurable or evaluable lesions; (ii) evidence of unresectable disease, organ metastasis, distant node metastasis, peritoneal dissemination detected by barium enema or laparotomy, or involvement of the adjacent organs confirmed by laparotomy; (iii) age ≤75 years; (iv) performance status (PS) on the Eastern Cooperative Oncology Group scale of 0–2; (v) adequate organ functions; (vi) no serious complications; (vii) no other active malignancies; and (viii) no prior chemotherapy. Characteristics of the 497 patients are listed in Table 2.

Table 1. Clinical outcomes of each chemotherapy regimen

Study no.	Regimen	*n*	RR	MST	2-year survival (%)	5-year survival (%)
8501	FTM	50	8	6.0	2 (4)	0
	UFTM	39	21	7.1	1 (3)	1 (3)
8804	5′P	49	35	8.1	8 (16)	2 (4)
8903	EAP	42	55	9.3	6 (14)	3 (7)
9001	FP	46	43	7.4	5 (11)	2 (4)
9205	UFTM	67	9	6.0	3 (4)	0
	FP	100	36	7.7	7 (7)	0
	5-FUci	104	12	6.7	7 (7)	3 (3)

RR = response rate; MST = median survival time (months). See text for the definitions of the regimens.

Table 2. Patient characteristics

	n = 497
Age (years): median (range)	61 (19–75)
Gender: male/female	364/133
PS: 0/1/2	175/236/86
Histological types: I/D/U	228/266/3
Macroscopic types: scirrhous/non-scirrhous	137/362
History of gastrectomy: +/−	84/413
Metastatic site	
Liver	236
Abdominal lymph node	232
Peritoneum	86
Others	70
No. of metastatic sites: 1/2/≥3	315/148/34

I/D/U = intestinal/diffuse/unknown; PS = performance status.

EVALUATION OF RESPONSES

Responses to chemotherapy were evaluated according to the standard World Health Organization criteria for measurable metastatic lesions (11). For primary lesions, the responses were evaluated according to the criteria proposed by the Japanese Research Society for Gastric Cancer (12) using either gastroscopy or barium gastrography. The responses to chemotherapy were confirmed by extramural review during each study and were adopted into the present analysis according to each case report form. Overall response was defined as the sum of the number of complete and partial responses.

STATISTICS

Survival times of all patients were calculated from the date of registration to the date of death from any cause, or to the last confirmation of survival, using the Kaplan–Meier method.

Of the 497 patients, only four (1%) patients were lost to follow-up. Survival was updated in February 2002, with a minimum follow-up period of 5 years for univariate and multivariate analyses. Univariate analyses were performed by log-rank testing using the following seven categories: (i) age >60 versus ≤60 years old; (ii) male versus female; (iii) PS 0 versus 1 or 2; (iv) macroscopically scirrhous-type cancer (Japanese classification type 4) versus non-scirrhous type; (v) histologically intestinal type versus diffuse type; (vi) with versus without history of gastrectomy; and (vii) one versus two versus three or more metastatic sites. Multivariate analysis of prognostic factors using a Cox proportional hazard model was carried out with these categorized variables to calculate relative risks and their 95% confidence intervals (CIs).

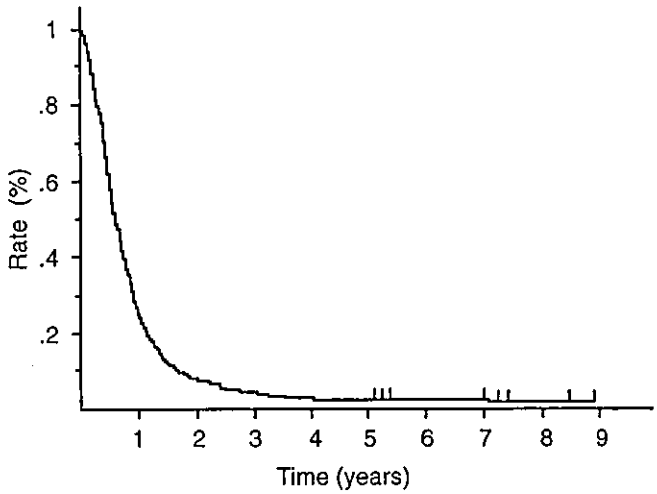

Figure 1. Overall survival of patients.

RESULTS

Patient Characteristics

Characteristics of the 497 patients are summarized in Table 2. Most of the patients had a good PS at registration, while 86 (17%) had a PS of grade 2. Histologically, 228 (46%) patients had an intestinal type of adenocarcinoma, 266 (54%) had a diffuse type and three had an unknown type. One hundred and thirty-seven patients (28%) had macroscopically scirrhous-type primary gastric tumors. Eighty-four (17%) patients had undergone gastrectomy before registration. The sites of metastases documented in the 497 case report forms were: abdominal lymph nodes in 232 (47%); liver in 236 (47%); peritoneum in 86 (17%), and others in 70 (14%) patients. The number of metastatic sites consisted of one in 315 (63%), two in 148 (30%) and three or more in 34 (7%) patients, respectively.

Response and Survival

Of the 497 patients, six (1%) achieved a complete response (CR) and 121 (24%) achieved partial responses, giving an overall response rate of 26%. The response rates in each regimen are listed in Table 1, ranging from 8% in the FTM group to 55% in the EAP group. Figure 1 shows survival curves of all 497 patients, indicating a median survival time (MST) of 7.2 months. The MSTs in each regimen are listed in Table 1, ranging from 6.0 to 9.3 months. Of the 497 patients, 39 (8%) and 11 (2%) have survived longer than 2 and 5 years, respectively. The numbers of 2- and 5-year survivors in each regimen are listed in Table 1.

Characteristics of Long-term Survivors

Twenty-six (67%) of the 39 2-year survivors responded to the initial chemotherapy. These 39 patients included 11 with para-aortic node metastasis alone as an 'unresectable factor'. All of the 39 patients had been classified into PS grades 0 or 1 at registration. Twelve patients had prior gastrectomy before starting chemotherapy. There were no significant differences in histological types between the 2-year survivors and the others.

Table 3. Characteristics of 5-year survivors

Age	G	PS	Macro	H	MS	Surg.	First R	Response 1st/2nd	Surv	Pre
75	M	0	N	D	Liver	–	5-FUci	CR/–	60	D
65	M	0	N	I	A-LN	B	5-FUci	PR/PR	61	A
46	M	0	N	D	A-LN	B	5-FUci	PR/–	63	A
55	M	1	N	I	Liver	–	UFT	PR/CR	65	A
47	M	0	N	I	A-LN	B	FP	CR/–	85	A
52	M	1	N	I	A-LN	–	5'FP	CR/–	86	D
57	M	1	N	D	A-LN	A	EAP	PR/–	87	D
53	M	0	N	D	A-LN	A	EAP	CR/–	88	A
49	F	0	N	D	A-LN	B	FP	NC/CR	90	A
58	M	0	N	I	A-LN, C-LN	A	EAP	CR/–	103	A
62	M	1	N	I	A-LN	A	5'FP	PR/–	108	A

G = gender; M = male; F = female; PS = performance status; Macro = macroscopic type; N = non-scirrhous; H = histology; I = intestinal; D = diffuse; MS = metastatic site; A-LN = abdominal lymph node; C-LN = cervical lymph node; Surg. = surgical resection (A = after chemotherapy; B = before chemotherapy); R = regimen (for definitions see text); CR = complete response; PR = partial response; Surv = survival (months); Pre = present status (A = alive; D = dead).

Characteristics of the 11 5-year survivors are summarized in Table 3. These patients consisted of eight with para-aortic node metastases alone as an 'unresectable factor', one with para-aortic and cervical node metastases, and two patients with only liver metastases. Ten of the 11 patients achieved overall responses to the initial chemotherapy: five patients achieved CR at the initial chemotherapy and one patient achieved CR by the second-line chemotherapy. One patient, who had not achieved an objective response to the initial chemotherapy (FP) achieved CR in the third line chemotherapy, consisting of 5-FU + doxorubicin + mitomycin C. Of the 11, eight patients received surgical resections, four patients before initiating the chemotherapy and four after achieving tumor regression

Table 4. Univariate analysis by each variable

Variable	*n*	MST	2-year survival (%)	5-year survival (%)	*P*-value
Age (years)					
<60	219	7.8	10.5	3.7	
≥60	278	6.8	5.8	1.1	0.04
Gender					
Male	364	7.2	8.2	2.7	
Female	133	7.2	6.8	0.8	0.9
Performance status					
0	175	9.9	11.0	4.0	
1	236	6.8	8.5	1.7	
2	86	5.1	0	0	<0.01
Histological type					
Intestinal	228	7.8	9.2	2.6	
Diffuse	266	6.5	6.8	1.9	0.3
Macroscopic type					
Scirrhous	137	6.0	4.4	0	
Non-scirrhous	360	7.6	9.2	3.1	0.04
History of gastrectomy					
Yes	84	8.3	14.3	4.8	
No	413	6.8	6.5	1.7	0.02
No. of metastatic sites					
1	315	8.3	9.5	3.2	
2	148	5.9	5.4	0.7	
≥3	34	5.4	2.9	0	<0.01

Table 5. Relative risk of prognostic factors

Variable	*n*	RR	95% CI	*P*-value
Age (years)				
<60	219	–		
≥60	278	1.16	0.97–1.40	0.2
Gender				
Male	364	–		
Female	133	0.93	0.75–1.14	0.5
Performance status				
0	174	–		
1	235	1.16	1.08–1.25	<0.01
2	85			
Histological type				
Intestinal	228	–		
Diffuse	266	1.13	0.97–1.30	0.11
Macroscopic type				
Scirrhous	137	–		
Non-scirrhous	360	1.27	1.02–1.25	0.04
History of gastrectomy				
Yes	84	–		
No	413	1.01	0.92–1.10	0.9
No. of metastatic sites				
1	315	–		
2	148	1.32	1.14–1.53	0.01
≥3	34			

Performance status and no. of metastatic sites are ordered categories.

in the initial chemotherapy, including two with a pathological CR in the surgically resected specimen. The remaining three patients did not receive surgical resection during the follow-up period. Ten of the 11 5-year survivors presented with no evidence of disease at 5 years, while two patients died after 5 years because the primary disease recurred.

Univariate and Multivariate Analyses

Results of the univariate and multivariate analyses are summarized in Tables 4 and 5. Univariate analysis revealed significantly better survival in patients in five categories: age <60 years, PS = 0, macroscopically non-scirrhous-type tumors, a prior history of gastrectomy and a small number of metastatic sites. Figure 2 shows the survival curves of the patients with only one metastatic site: 77 with abdominal lymph nodes, 44 with peritoneal tumors and 117 with liver metastases alone. Their MSTs were 9.6, 8.2 and 7.7 months, with 2-year survival rates of 14.3, 15.9 and 6.8%, and with 5-year survival rates of 10.4, 0 and 1.7%, respectively. One hundred and seventeen patients with only liver metastases had the worst MST among the three groups and showed significantly poorer survivals than the remaining patients ($P = 0.04$). Seventy-seven patients with only abdominal lymph node metastases had a remarkably higher 5-year survival rate than other groups, while their MSTs and 2-year survival rates were similar to those of 44 patients with only peritoneal metastases.

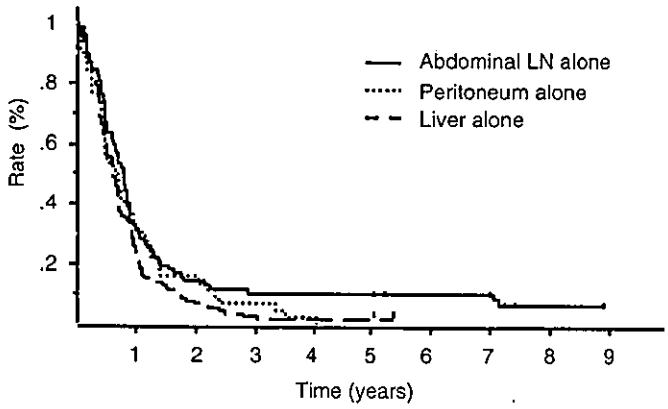

Figure 2. Survival of patients with a single metastatic site: 77 patients had a metastasis to an abdominal node, 117 had a liver metastasis and 44 had a peritoneal metastasis. LN, lymph node.

Multivariate analysis revealed that the presence of only one metastatic site, a macroscopically non-scirrhous-type tumor

and a good PS score were each significantly associated with better prognosis (Table 5).

DISCUSSION

We have already reported the preliminary long-term results of 226 patients with unresectable gastric cancer and treated with systemic chemotherapy, which revealed 2- and 5-year survivals of 10 and 4%, respectively (10). In the present analysis, an additional 271 patients registered in the subsequent phase III trial (9205) were included to confirm the previous results and to carry out multivariate analysis for prognosis. With regard to the long-term results, 2- and 5-year survivals in the additional 271 patients were 6 and 1%, respectively. These survivals were lower than those obtained previously (10), where long-term survivals in cisplatin (CDDP)-containing regimens (8804, 8903 and 9001) were better than non-CDDP-containing regimens (8501). One possible reason for the lower long-term survivals in trial 9205 might be that only one of the three arms included a CDDP-containing regimen (FP). However, this superiority of a CDDP-containing regimen was not observed in the additional 271 patients enrolled into the phase III study (9205): 2- and 5-year survivals in the FP group were 7 and 0%, whereas those in the 5-FUci group were 7 and 3%, respectively. Based on these results, the superiority of CDDP-containing regimens in the phase II series (8804, 8903 and 9001) in terms of long-term survival might have been caused by selection bias: for example, the incidence of patients with a single metastatic site was 77% in phase II and 52% in phase III.

Was the long-term survival of a few patients truly achieved by chemotherapy, or was it simply related to the natural history of these patients? Because there have been no prospective reports using adequate sample sizes on the long-term survival of patients not treated with chemotherapy, it is hard to establish the effectiveness of chemotherapy for long-term survival. However, there have been two randomized trials comparing best supportive care with combination chemotherapy (1,2). Although these studies had only a few patients, no patient treated solely with supportive care survived longer than 1 year. Additionally, most of the long-term survivors in the present analysis achieved good responses to chemotherapy, particularly the 5-year survivors: 10 of the 11 patients were alive with no evidence of disease at 5 years. These results thus support the value of chemotherapy for achieving long-term survival.

Because the case report forms in the earlier study frequently lacked laboratory reports of serum data including tumor markers, these data were excluded from this multivariate analysis. Univariate analysis revealed that there were significant differences in survival in terms of PS grade, numbers of metastatic sites, having a history of gastrectomy, age and macroscopic tumor type. However, multivariate analysis showed there were only three variables significantly and independently associated with a good prognosis: having a better PS grade, having fewer metastatic sites and the presence of macroscopically non-scirrhous-type tumors. Better PS grade and fewer metastatic sites are also known to be better prognostic factors in patients with advanced colorectal cancer treated with chemotherapy (13). In addition, patients with macroscopically scirrhous-type tumors showed significantly poorer survival than those with non-scirrhous types, and this seems to be specific for patients with gastric cancers. Scirrhous tumors are also known to lead to poorer survival than other macroscopic types in patients treated by surgical resection (14). Thus, these forms of tumors appear to be especially malignant and exhibit a higher resistance to chemotherapeutic agents.

Another objective of this study was to clarify the characteristics of the long-term survivors. The 11 5-year survivors had some specific characteristics. All patients had good PS grades of 0 or 1 and macroscopically non-scirrhous-type tumors. Ten had only one metastatic site, achieved a CR through the initial chemotherapy and had no evidence of disease at 5 years. Another significant characteristic was that eight of the patients had only a para-aortic node metastasis as an unresectable factor. In the whole study series, 77 such patients had significantly better 5-year survival (10.4%) than the other patients with single metastatic sites, such as in the liver or peritoneum. Thus patients with para-aortic node metastases alone have a greater chance of achieving long-term survival than other patients; this suggests that potentially curative strategies such as adjuvant surgery may be effective for them. A phase II study of this strategy for this subpopulation (neoadjuvant chemotherapy followed by surgery) by the JCOG is now underway.

The role of surgery in patients with potentially incurable disease remains controversial. Although patients with prior surgery showed better survival than others in the univariate analysis, this was not found in the multivariate analysis. This might have been caused by 'leading bias'—early detection of recurrence—because of periodic follow-up surveys after surgery. It is also difficult to evaluate the role of adjuvant surgery after achieving downstaging by chemotherapy because of the small number of such cases. However, of the 11 5-year survivors, eight received surgical resections for primary sites, including four patients with adjuvant surgery. Thus adjuvant surgery might have value, particularly for patients with para-aortic node metastasis alone, if they achieve downstaging by chemotherapy. Of course, these advantages should be evaluated further in the ongoing neoadjuvant study.

In conclusion, there were a few long-term survivors in patients with unresectable gastric cancer treated with chemotherapy. This suggests that some patients with only abdominal lymph node metastases may achieve long-term survival with successful chemotherapy. Better PS scores, small numbers of metastatic sites and macroscopically non-scirrhous-type tumors were independent favorable factors for survival in the multivariate analysis.

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REVIEW ARTICLE

Atsushi Ohtsu

Chemoradiotherapy for esophageal cancer: current status and perspectives

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Abstract The optimal role of chemoradiotherapy in the multimodality treatment of esophageal cancer is still controversial. According to a series of clinical trials, definitive chemoradiotherapy is considered the standard of care for patients with medically inoperable or surgically unresectable esophageal cancer. This modality provides survivals comparable to those in Western series of surgery alone and is one of the standards of care even for resectable-stage disease. Recent reports of primary chemoradiotherapy from Japan suggest survival comparable to that of surgery in Japanese patients with stage I disease, but radical surgery is still the standard treatment for T2–3NanyM0 disease in Japan. However, it is clear that this approach has limitations in treatment outcomes. Trimodality therapy, i.e., preoperative chemoradiotherapy followed by surgery, is more favored than surgery alone in clinical practice, particularly in patients with adenocarcinoma, although current data from randomized trials are insufficient to support this approach. To improve the local control rate of chemoradiotherapy, intensification of the radiation dose has been attempted, but this has failed to demonstrate any superiority in terms of local control or survival. The addition of new agents, including molecular targeting agents, to the current standard chemoradiotherapy has shown more promising results and warrants further investigations in future studies. Salvage treatment for patients who do not achieve a complete response (CR) is necessary to improve the overall treatment results. Salvage surgery, as well as endoscopic resection, in selected patients, may provide an improvement in survival. Until high rates of local control can be consistently achieved with chemoradiotherapy alone, these salvage treatments will be an integral component of multimodality treatment for esophageal cancer, and should be active areas for clinical investigations.

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Key words Esophageal cancer · Chemoradiotherapy · Combined modality treatment

Introduction

The optimal management of esophageal cancer is still controversial. In regard to nonsurgical treatments, historical series of external-beam radiation alone have reported 5-year survival rates of 0%–10%.[1–3] In the Radiation Therapy Oncology Group (RTOG) 85-01 randomized trial comparing radiation therapy alone (64 Gy) with definitive chemoradiotherapy, consisting of 5-fluororuracil (5-FU), cisplatin, and concurrent radiation (50 Gy), there was a significant survival difference in favor of the combined arm (0% vs 27% 5-year survival).[4] Based on these results, the current standard of care for patients who are not suitable candidates for surgery, or who do not wish to have surgery, is definitive chemoradiotherapy; radiation therapy alone should be reserved for palliation or for patients who are medically unable to receive chemotherapy.

Various combined modality approaches have been attempted to improve the treatment outcomes of esophageal cancer. Largely, there are three approaches for combined modality: primary surgery with adjuvant chemotherapy or chemoradiotherapy, primary definitive chemoradiotherapy with or without salvage surgery, and preoperative chemoradiotherapy followed by surgery. In the chemoradiotherapy, the radiation dose is usually limited to 40–45 Gy when used in a preoperative setting, and it is increased to 50–60 Gy when used as a definitive treatment. Many randomized trials comparing these multimodality treatments have been reported, mostly from Western countries; however, no consensus has been established yet worldwide.[5–7] When considering the results from Western countries, there are various obstacles in interpreting the findings in relation to practice in Japan, as there are great differences in modes of surgical resections and survival results between Western countries and Japan as well as differences in tumor biology, in rates of squamous cell carcinoma and adenocarcinoma.

Table 1. Treatment results of definitive chemoradiotherapy in randomized trials

	Chemotherapy	RT (Gy)	*n*	2-Year survival	3-Year survival	*P* Value
RTOG 85-01	FP	50	61	38%	30%	<0.0001
	Control	64	62	10%	0%	
RTOG 94-05	FP	50	109	40%	NR	NS
	FP	64	109	31%	NR	

FP, 5-fluorouracil + cisplatin; NR, not reported; NS, not significant; RT, radiotherapy

Table 2. Randomized trials of preoperative chemoradiotherapy + surgery versus surgery alone

Author	*n*	Histology	Treatment	pCR	MST (months)	3-Year survival	*P* Value
Bosset et al.[19]	282	100% Squamous cell carcinoma	CRT + S	26%	19	36%	0.8
			S	0%	17	36%	
Walsh et al.[18]	113	100% Adenocarcinoma	CRT + S	25%	16	32%	0.01
			S	0%	11	6%	
Urba et al.[20]	100	75% Adenocarcinoma 25% Squamous cell carcinoma	CRT + S	28%	17	30%	0.15
			S	0%	17	15%	

pCR, pathological complete response; MST, median survival time; CRT, chemoradiotherapy; S, surgery

The findings of a comprehensive review of the recent literature on chemoradiotherapy for the treatment of esophageal cancer are presented here.

Overview of chemoradiotherapy based on the results of clinical trials

Definitive chemoradiotherapy

Although there have been several trials comparing radiation therapy alone with chemoradiotherapy, most of the studies used suboptimal doses of radiation therapy or inadequate systemic chemotherapy.[8-11] The only trial which was designed to administer adequate chemotherapy with an optimal dose of radiotherapy was the RTOG 85-01 trial (Table 1).[4,11] In this study, patients in the radiation-alone group received irradiation alone, at a total dose of 64 Gy, and those in the chemoradiotherapy group received continuous infusion of 5-fluorouracil (5-FU; 1000 mg/m^2 per day for 4 days), cisplatin (75 mg/m^2, day 1), and concurrent irradiation, at a total dose of 50 Gy (2 Gy/day; 25 fractions). Histologically, the majority (82%) of the patients registered had squamous cell carcinoma. This study revealed a significant improvement of survival in terms of both median survival times (14 months vs 9 months) and 5-year survival (27% vs 0%; $P < 0.001$) in favor of chemoradiotherapy. With a minimum follow-up period of 5 years, the 8-year survival rate of the chemoradiotherapy group was 22%.[12] This study established definitive chemoradiotherapy as the standard of care for the nonsurgical management of esophageal cancer. However, local failure remained a major issue: 45% of the patients in the chemoradiotherapy group developed local failure.

To improve the local control rate, the intergroup randomized trial (INT 0123/RTOG 94-05) was conducted.[13] In this study, a slightly modified RTOG 85-01 chemoradiotherapy regimen was used as the control arm and was compared with an intensified dose, of 64.8-Gy radiation therapy, with the same chemotherapy. The modifications to the original RTOG 85-01 regimen were: using 1.8-Gy fractions to a total of 50.4 Gy, treating patients with 5-cm proximal and distal margins with 50.4 Gy, and chemotherapy being delivered every 4 weeks. This trial also included a majority (85%) with squamous cell carcinoma. However, no significant differences in 2-year survival (40% in the control arm vs 31% in the higher-radiation-dose arm) or in local failure and/or local persistence rate of disease (52% vs 56%) were observed in this study. These results demonstrated that intensification of the radiation dose did not improve the results of chemoradiotherapy.

Despite the failure of improvement by intensification of the radiation dose, this survival outcome from definitive chemoradiotherapy appeared to be comparable to that of primary surgery in the West.[14,15] However, no randomized trials comparing surgery with definitive chemoradiotherapy have been published, and accordingly, little is known about their comparative outcomes, although there have been a few series of retrospective comparisons that suggested similar survivals in both groups.[16,17]

Preoperative chemoradiotherapy followed by surgery in comparison with surgery alone

To improve surgical outcomes, preoperative chemoradiotherapy has been extensively investigated, as compared with surgery alone, in randomized trials although these studies have produced conflicting results (Table 2).[18-20] Walsh et al.[18] reported a randomized trial comparing preoperative chemoradiotherapy followed by surgery with surgery alone in 113 patients with adenocarcinoma of the esophagus. Radiation, at a total dose of 40 Gy in 15 frac-

Table 3. Randomized trials of chemoradiotherapy with and without surgery

Study	Stage	Treatment	*n*	SM	MST (months)	3-Year survival	*P* Value
French	T3M0	CRT	130	1%	19.3	31%	0.56
Responders only		CRT + S	129	9%	17.7	29%	
German	T3-4M0	CRT	88	2%	15.2	24% (54%)	0.06
		CRT + S	89	9%	16.3	31% (54%)	

Figures in parentheses are results of patients who responded to chemoradiotherapy
SM, surgical mortality; MST, median survival time; CRT, chemoradiotherapy; S, surgery

tions, was delivered concurrently with chemotherapy consisting of 5-FU, at 15 mg/kg per day for 5 days and cisplatin at 75 mg/m^2 on day 1. Significantly better 3-year survival (32% vs 6%) was observed in favor of the trimodality arm. However, there was a major criticism, of the high surgical mortality rate of 9% and the low 3-year survival of 6% in the surgery-alone arm.

Urba et al.[20] have also reported the results of a randomized trial comparing trimodality therapy with surgery alone, in 100 (75% with adenocarcinoma) patients with esophageal cancer. Patients were randomly allocated to either preoperative 5-FU, cisplatin, vinblastine, and radiation therapy (45 Gy) followed by transhiatal esophagectomy or surgery alone. Although there was a trend for improved survival (30% vs 15% at 3 years) for patients treated with the trimodality therapy, the difference did not reach statistical significance. Two other similar randomized trials failed to demonstrate a survival advantage of preoperative chemoradiotherapy.

Based on these results, there still remain controversies in regard to the survival advantage of preoperative chemoradiotherapy over surgery alone. Limitations of sample sizes in these studies, and the high mortality rate after preoperative chemoradiotherapy may be the major causes of the negative results. However, it seems likely that preoperative chemoradiotherapy is a reasonable treatment approach, particularly in patients with adenocarcinoma, although a definitive answer has not been obtained yet.

Preoperative chemoradiotherapy followed by surgery in comparison with definitive chemoradiotherapy

Two large randomized trials examining whether or not surgery is necessary after chemoradiotherapy were reported at the annual meetings of the American Society of Clinical Oncology in 2002 and 2003 (Table 3). The first study was reported from France (FFCD 9102).[21] This study included patients with T3NanyM0, who received, firstly, chemoradiotherapy comprising two courses of 5-FU and cisplatin with concurrent radiation therapy ranging from 30 to 46 Gy, and then were randomly allocated to receive surgery or additional chemoradiotherapy (three courses of the same chemotherapy and 20 Gy of irradiation) if they had responded to the initial chemoradiotherapy. A total of 451 patients were enrolled, with 259 patients who responded to the initial chemoradiotherapy entered into the randomized stage of the study. No significant differences in overall survival were observed between the surgery and additional chemoradiotherapy arms. Median survival times and 2-year survival rates in the two arms were 17.7 months and 34%, respectively, in the surgery arm, and 19.3 months and 40%, respectively, in the additional-chemoradiotherapy group. Mortality rates within 3 months were higher in the surgery group than in the chemoradiotherapy group (9% vs 1%). However, there were no significant differences in quality of life between the two arms, although the scores were superior in the chemoradiotherapy group during the first 2 years of treatment. The second study was reported from Germany. [22] Patients with T3–4NanyM0 squamous cell carcinoma were randomized to receive chemoradiotherapy followed by surgery or definitive chemoradiotherapy alone. The chemoradiotherapy consisted of three cycles of chemotherapy (5-FU + leucovorin + etoposide + cisplatin) followed by chemoradiotherapy (etoposide + cisplatin + irradiation up to 40 Gy for the trimodality group, or up to 60 Gy for the chemoradiotherapy group). A total of 177 patients were registered for the study. Mortality rates during the treatment were higher in the trimodality arm than in the chemoradiotherapy group (9% vs 2%). Survival differences between the groups showed a tendency in favor of the trimodality arm ($P = 0.06$) and the trend appeared more remarkable after 3 years, though the difference did not reach statistical significance. However, in patients who responded to the initial chemoradiotherapy, there were no obvious differences in survival between the two arms, similar to the result seen in the FFCD 9102 trial (Table 3).

Toxicity of chemoradiotherapy

With the addition of synchronous chemotherapy to radiotherapy, acute treatment-related toxicity is significantly increased. The major toxicities are myelotoxicity and esophagitis. In the RTOG 85-01 trial, grade 3 or 4 esophagitis occurred in 33% of patients receiving chemoradiotherapy, compared with 18% in those receiving radiotherapy alone.[11] The risk of myelosuppression increases with an increasing number of chemotherapy agents or with increases of dose intensity. When the standard chemotherapy regimen, 5-FU and cisplatin, is incorporated into chemoradiotherapy, the treatment is usually safe. However, in patients who received mitomycin C, vinblastine, paclitaxel, or etoposide in addition to 5-FU and cisplatin, high rates of severe myelotoxicity have been reported.[23–26]

Table 4. Late toxicity of definitive chemoradiotherapy in 78 patients achieving a CR

	Grade (G)			
	2	3	4	≥G3 (%)
Pleural effusion	7	8	–	10.3
Pericarditis	8	7	1	10.3
Heart failure	–	–	2	2.6
Radiation pneumonitis	1	3	–	3.8

Regarding the late toxicity of chemoradiotherapy, our group has reported its incidence and outcomes in 78 patients who achieved a complete response with definitive chemoradiotherapy.[27] Major late toxicities included pleural effusion, pericarditis, and radiation pneumonitis: the incidences of grade 3 or 4 of these toxicities were 10.3%, 10.3%, and 3.8%, respectively (Table 4). The median times to the onset of grade 3 or 4 pleural effusion, pericarditis, and pneumonitis were 15, 18, and 5 months, respectively, from the initiation of chemoradiotherapy. In total, 8 patients died without cancer recurrence, and their causes of death may have been related to cardiopulmonary toxicity. One of the reasons for the significant late toxicity may have been the wide elective nodal irradiation, of up to 40 Gy with anteroposterior opposed portals, which means that more than 60% of the entire heart volume received at least 40 Gy. Additional investigation to minimize toxicities to normal tissues is warranted.

When chemoradiotherapy was combined with surgery, the reported postoperative mortality ranged from 0 to 29%, with a mean value of 9%.[28] Adult respiratory distress syndrome, anastomotic leakage and breakdown, pneumonia, and sepsis were the most common causes of death following esophagectomy.

Current status of chemoradiotherapy by stage

Stage I disease

In the Western studies described above, few patients with stage I disease were included, and the impact of chemoradiotherapy for this stage has not been clarified. From Japan, Ura et al.[29] reported a retrospective series of definitive chemoradiotherapy in 73 patients with stage I disease. There were 68 (93%) complete responses, and the remaining 5 patients with residual tumor were successfully treated with endoscopic resection (ER) or surgery. Salvage ER or surgery was also safely indicated for recurrent local tumors. Ura et al.[29] achieved 3- and 5-year survival rates of 80% and 77%, respectively, which are comparable to those for ordinary surgery. Similar results have been reported from a multiinstitutional prospective study from the Japan Clinical Oncology Group (JCOG 9708) in patients with stage I disease.[30] A total of 72 patients were registered, and a 96% complete response rate was achieved with definitive chemoradiotherapy. Patients who developed recurrence were successfully treated with ER and surgery. The 2-year survival and recurrence-free survival were 93%, and 75%, respectively. These results are comparable to those for primary surgical resections,[31] and chemoradiotherapy may be a standard treatment option, although salvage ER or surgery is necessary. A randomized trial comparing primary chemoradiotherapy with surgery for stage I disease is now being planned by the JCOG.

Stage II–III (non-T4)

Controversies still remain in regard to the primary treatment of resectable disease. Based on the results from randomized trials, definitive chemoradiotherapy is considered a standard treatment for the nonsurgical approach and the survival results are comparable with Western series of surgical resections. However, it is clear that both the nonsurgical and surgical approaches have limited success, with 3- to 5-year survivals of 20% to 30%. Trimodality therapy, i.e., preoperative chemoradiotherapy followed by surgical resection, is considered the preferred modality, particularly in patients with adenocarcinoma, although a definitive advantage over surgery alone has not been confirmed yet. Other major concerns are whether the prognosis improves after surgery in patients who have residual tumors after definitive chemoradiotherapy, and whether there is better local control with the trimodality therapy. To elucidate this issue, useful information was obtained from the two European (French and German) randomized trials that compared chemoradiotherapy with and without surgery.[21,22] Although the target populations were slightly different (only T3 in the French trial and T3-4 in the German trial), the two studies showed similar results: 9% surgical mortality in both studies and no significant differences in survival between the two arms in patients who responded to the initial chemoradiotherapy. These results suggest that additional surgery has little impact on survival if patients achieve an objective response to the initial chemoradiotherapy. However, the German study, which included nonresponsive patients, tended to show borderline differences in survival in favor of additional surgery, while the French study also demonstrated better local control in the surgery group. These results may support the clinical utility of additional surgery. The National Comprehensive Cancer Network (NCCN) practice guidelines in the United State indicate that both esophagectomy and chemoradiotherapy with doses of 50–50.4 Gy are considered to be the standard treatment.[7] The recommendations also include surgery after chemoradiotherapy and adjuvant chemoradiotherapy after primary surgery, particularly in patients with adenocarcinoma, as recommended approachs, although these modalities are still investigational.

In Japan, compared with the West, there are significant differences in tumor biology and surgical treatments: histologically, in Japan, most tumors are squamous cell carcinoma, and radical surgery with extensive nodal dissection is commonly indicated. A retrospective comparison of surgical resection and definitive chemoradiotherapy at our insti-

tution revealed comparable survivals,[17] and these results seem to be similar to surgical outcomes at other Japanese institutions.[32] However, the recent JCOG randomized trial comparing radical surgery alone with radical surgery plus adjuvant chemotherapy (JCOG 9204) has reported survivals superior to those in retrospective series: the 5-year survivals of the surgery-alone and surgery- plus-adjuvant chemotherapy arms were 52% and 61%, respectively.[33] This study was based on postoperative registration, in which surgical mortality and patients with poor condition after surgery were excluded, and, therefore, there may have been some selection biases toward superior survival. However, these results are better than those for definitive chemoradiotherapy in Japan and for Western surgical series. To date, radical surgical resection with adjuvant chemotherapy is considered the standard care for this stage; for patients who are not suitable candidates for surgery, or for those who do not wish to have surgery, primary chemoradiotherapy is considered the standard care.

Unresectable T4/M1 lymphnode (LYM) disease

For patients with T4 disease, although aggressive surgical resection has been attempted in Japan, the outcome was very poor, with 5-year survival rates of less than 10% and high mortality and morbidity rates.[34] Ando et al.[32] reported outcomes of surgery in a sample of 419 patients from a single Japanese institution. In their series, although more than half of the patients underwent radical dissection, no patients with T4 disease survived for longer than 5 years. Nevertheless, there have been some Japanese reports of primary surgery for M1 LYM disease that resulted in 5-year survival rates of 14%–25%.[35,36] These results may support the use of surgery for M1 LYM disease. However, these data were based on pathological stage and it is unclear whether all clinical M1 LYM disease was included. Therefore, controversy remains regarding the indication of primary surgery for clinically relevant M1 LYM disease.

Several clinical studies of chemoradiotherapy specific to this stage have been carried out in Japan. Our group conducted a multicenter phase II study of concurrent chemoradiotherapy, consisting of 5-FU and cisplatin with 60 Gy of irradiation, for unresectable T4 and/or M1 LYM squamous cell carcinoma of the thoracic esophagus.[37] Fifty-four patients participated in the study: there were 36 patients with T4 disease and 18 patients with non-T4 (only M1 LYM) disease. Of the 54 patients, 18 (33%) achieved a complete response: 9 (25%) with T4 disease and 9 (50%) with non-T4 disease. Major toxicities were leukocytopenia and esophagitis, and there were four (7%) treatment-related deaths. The median survival time was 9 months, and the 3-year survival rate was 23%. We concluded that, despite its significant toxicity, this combined modality seemed to have curative potential, even in patients with locally advanced carcinoma of the esophagus. To confirm long-term outcomes, survival and toxicity data were updated in February 2003, which was over 5 years after the last accrual. Nine patients had survived for more than 5 years, with an actuarial 5-year survival rate of 17% (9/54): the rates were 14% (5/36) in patients with T4 disease and 22% (4/18) in those with non-T4 disease (unpublished data). Similar survival outcomes were obtained in retrospective analyses of subsequent patients treated in daily practice.[38,39] Nishimura et al.[40] reported a prospective trial of definitive chemoradiotherapy, consisting of 5-FU, cisplatin, and concurrent external-beam radiation, at a total of 60 Gy, for 28 patients with T4 esophageal cancer with or without fistulae. This study provided a complete response rate of 32%, and 2-year survival of 27% in patients with stage III disease (T4NanyM0), which appeared to be comparable to the results in our study.

Based on these recent results, mentioned above, chemoradiotherapy should be the primary treatment for T4 disease, independently of whether it will be followed by surgery. Outcomes of these studies, showing 2- to 3-year survival rates of approximately 20%, are obviously better than outcomes for palliative therapies; these survival rates could be a landmark in the treatment of T4 disease. Another major concern is whether the patients' prognoses improve following surgery. To elucidate this issue, useful information was obtained from the two European randomized trials that compared chemoradiotherapy with and without surgery.[21,22] As mentioned previously, these results may support the clinical efficacy of additional surgery, although this approach is still investigational.

Future perspectives in chemoradiotherapy

Improving local control

The major issue in primary chemoradiotherapy at present is the insufficient local control rate. Regarding this issue, intensification of radiation dose has been attempted in the INT 0123 trial, but it failed to improve the local control rate.[13] Other trials with accelerated or hyperfractionation radiation methods also showed no benefit in local control or survival, whereas there were significantly higher incidences of severe esophagitis.[41–43] These results showed the limitations of intensifying the radiation dose. The addition of new agents, other than 5-FU plus cisplatin, may be more promising. Preliminary results of adding paclitaxel to the standard chemoradiotherapy regimen showed encouraging results, with a pathological complete response rate of around 70%,[44] which warrants further investigation. The use of molecular targeting agents in combination with chemoradiotherapy could be optimal, because their toxicity profiles are clearly different from those of cytotoxic agents. In the field of head and neck cancer, cetuximab, a monoclonal antibody to epidermal growth factor receptor (EGF-R), in combination with radiation therapy, significantly prolonged survival in patients with locally advanced disease as compared with radiation alone.[45] Gefitinib, a post-EGF-R tyrosine kinase inhibitor, as monotherapy, has also shown activity against esophageal cancer.[46] Investigation of these new agents in addition to the

current standard chemoradiotherapy will be a major focus in future studies.

Salvage treatment after failure of definitive chemoradiotherapy

The survivals of patients who do not achieve a complete response with definitive chemoradiotherapy are dismal, and salvage treatment for such patients is indicated to improve the overall treatment results. The current standard radiation dose in definitive chemoradiotherapy is 50 Gy, which seems not significantly different from the doses used preoperatively (40–45 Gy). Some small studies have shown the feasibility and efficacy of salvage surgery.[47,48] Reduction of the high mortality after chemoradiotherapy is another important issue that warrants investigation. A reliable means of identifying those who are unlikely to achieve a pathological complete response is required. Some biological markers can predict prognosis and response to chemoradiotherapy, though these should be confirmed in a prospective manner in studies with a large sample size.[49,50] The optimal timing and modes of salvage surgery should also be investigated in future studies. In our practical experience,[51] when residual or recurrent tumors were limited to within the submucosal layer, ER was a safe and effective salvage treatment, and these endoscopic treatments also warrant further investigations. Until high rates of local control can be consistently achieved with chemoradiotherapy alone, these salvage treatments appear to be an integral component of multimodality treatment for esophageal cancer, and they should be active areas for clinical investigations.

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Original article

Japanese nationwide post-marketing survey of S-1 in patients with advanced gastric cancer

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Abstract

Background. **It is likely that there are some discrepancies in the safety and efficacy results for anticancer agents between those shown in registration studies for approval and those shown in clinical practice after market release. The aim of this survey was to confirm the safety and efficacy of S-1 for advanced gastric cancer after market release.**

Methods. **After the approval of S-1 in 1999, all patients had to be registered with the manufacturer for a post-marketing survey, according to the government recommendation. All patients were monitored for safety and survival. The data for all registered patients were updated 1 year after each registration.**

Results. **During this survey, a total of 4177 patients with advanced gastric cancer were registered. The incidences of all adverse events and of grade 3 or worse adverse events in the 3808 patients evaluable for safety were 74.3% and 25.0%, respectively. In patients with lower creatinine clearance at baseline, the incidences of adverse reactions were higher for all grades combined, as well as for grades 3 or worse. There were 90 (2.4%) early deaths (within 30 days of the initiation of the treatment) and 5 (0.1%) deaths possibly related to the treatment. The median survival time and the 1-year survival rate for all patients evaluable for efficacy (n = 3801) were 8.3 months (95% confidence interval [CI], 8.0–8.6 months) and 33.3% (95% CI, 31.8–34.9%), respectively.**

Conclusion. **This nationwide survey confirmed that the safety and efficacy profiles of S-1 were similar to those seen in the registration study. These results have proven the utility of this post-marketing survey in assessing the reproducibility of the safety and efficacy results obtained from prior clinical studies.**

Key words Gastric cancer · S-1 · Post-marketing survey

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Introduction

S-1 is a novel oral fluoropyrimidine agent that exploits the biochemical modulation of 5-fluorouracil (FU) pharmacokinetics. S-1 contains tegafur (FT), gimestat (CDHP), and otastat potassium (Oxo) at a molar ratio of 1:0.4:1. This agent was initially developed by Taiho Pharmaceutical Company, Tokyo [1], for gastric cancer in Japan. In the two phase II registration studies, this agent demonstrated excellent activity for gastric cancer, with response rates of 49% (25/51) and 40% (20/50), respectively [2,3]. The toxicity profile of this agent was mild: less than a 10% incidence of grade 3 or 4 adverse events and no treatment-related deaths. Based on these results, the agent was approved for the treatment of gastric cancer by the Ministry of Health, Labor, and Welfare (MHLW) of Japan, in 1999.

There have been several scandals in investigational trials of new drugs in Japan. In the development of irinotecan (CPT-11), which was first developed in Japan, there were some treatment-related deaths during the registration study: 20 of 477 patients died of toxicity during phase I and II clinical trials carried out between 1986 and 1990. This was not revealed in clinical trial publications or by MHLW staff, but was exposed instead by a newspaper, in 1993 [4]. These issues prompted the MHLW to adopt new "Good Clinical Practice (GCP)" guidelines for new drug approval, in 1997. Although these guidelines require strict safety monitoring with source document verifications and audit by the company, new anticancer agents are approved based on the results of two independent phase II studies. Because limitations on obtaining safety information are inevitable before approval, the MHLW recommended the use of nationwide post-marketing surveys for safety monitoring after the market release of a new drug. In accordance with the recommendations of the MHLW, Taiho Pharmaceutical Company conducted the present survey, with the goal of enrolling up

to 3000 patients in Japan. Before starting the post-marketing survey, the company contracted with a total of 757 participating institutions in Japan. This agent was not provided to any non-participating institution until completion of this survey.

Patients and methods

Contract with institutions

For the company to contract with an institution for this survey, the following requirements had to be met: availability of at least one attending physician who had sufficient experience of chemotherapy and who could undertake monitoring of patients at least once in 2 weeks, and the institution had to have the capability for immediate and adequate treatment of potential serious adverse events. All patients were monitored by the company, with a case report form filled out by each physician.

Registration

To promote the safe use of S-1, the company prepared guidelines for appropriate use, based on the previous registration studies. The guidelines ("appropriate-use" criteria) consisted of the following requirements for patients: having unresectable or recurrent gastric cancer; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or better; WBC of 3500–12000/μl; neutrocytes, 2000/μl or more; hemoglobin, 9.0 g/dl or more; platelets, 100000/μl or more; and total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) within two times the upper limit, and serum creatinine within the normal upper limit. For patients who failed some of the above criteria, administration of this agent was allowed, under careful observation, if the abnormal findings met the following criteria ("careful-use" criteria): ECOG PS within 3; WBC, 2000–3500/μl; neutrocytes, 1000–2000/μl; hemoglobin, 8.0–9.0 g/dl; platelets, 75000–100000/μl; total bilirubin, two times the upper limit to 3.0 mg/dl; AST and ALT, two times the upper limit to 150 IU/l, and serum creatinine, normal upper limit to 1.5 mg/dl.

All patients were required to give their informed consent and had to receive this agent as single-agent therapy. The patients were registered on a registration form completed by the physicians and the forms were sent to Taiho Pharmaceutical Company via facsimile. After confirmation of the registration, the company provided the agent to be given to the patients.

Treatment

S-1 was administered according to the treatment schedule for the registration studies. The initial doses were assigned on the basis of body surface area (BSA), as follows: 80 mg/day for BSA less than 1.25 m^2; 100 mg/day for BSA less than 1.5 m^2, and 120 mg/day for BSA of 1.5 m^2 or more. The treatment schedule consisted of 28 consecutive days of twice-daily administration (after breakfast and dinner) followed by a 2-week rest. This schedule was repeated every 6 weeks until the occurrence of disease progression, unacceptable toxicities, or patient's refusal. Modifications of dose and schedule were carried out by each physician according to the procedures in the previous registration studies, but without being regulated by the company.

Monitoring

Site-visit monitoring by the company was conducted regularly once a month. The case report forms were also collected monthly and were analyzed immediately by the company, followed by a report sent to the MHLW, once every 6 months. Adverse events were graded according to the toxicity criteria of the Japan Society for Cancer Therapy [5], which were modified from the criteria devised by the WHO. Serious or unexpected events were monitored throughout all administered courses, while other events were evaluated during the first two courses.

Safety analysis

Because this survey was carried out after market release, it included a few patients who were ineligible according to the "appropriate-use" guidelines mentioned in the "Registration" section, who were, however, administered the agent at the discretion of physicians. Although these patients seemed to be inappropriate for any chemotherapy, the company could not dissuade such inappropriate use in general settings. For safety analysis, all patients registered were classified into three groups according to the patients' baseline background: an "appropriate group", whose baseline data also met the eligibility criteria for the registration studies; a "careful-use" group, who needed careful observation as a condition of receiving the chemotherapy; and an "inappropriate" group, consisting of the remaining patients who failed the careful-use criteria. Baseline creatinine clearance was calculated, using the Cockcroft–Gault formula [6], for the precise evaluation of safety in patients with renal impairment.

Survival updating

The survival data of all patients registered were updated at 1 year after each registration and compared with the corresponding values in the previous phase II studies before approval; namely, the median survival time

(MST) of 8.0 months and 1-year survival rate of 36.6% [2,3].

Statistics

Cox proportional hazard analysis was employed to determine correlations between patients' baseline background and the incidence of all toxicities as well as the incidence of observed toxicities worse than or equal to grade 3. Patients were categorized into two groups by their eligibility status at baseline: "appropriate" group and a combination of the "careful-use" + "inappropriate" groups. Survival time was calculated from the initial date of the first course to the date of death, or the last confirmation of survival, using the Kaplan–Meier method.

Results

Patient characteristics

During the period between March 1999 and March 2000, a total of 4177 patients were registered for this survey from 757 institutions all over Japan. Of the 4177 patients, 286 did not actually receive the study agent, and 62 patients received S-1 administered outside the conditions of the contract between the company and the institution. There were also 12 double registrations and 9 patients whose case reports were not returned by their respective institutions, leaving a total of 3808 patients evaluable for safety. Another 7 patients in whom the study agent was administered for cancers other than gastric cancer were excluded from the efficacy analysis. Baseline patient characteristics are shown in Table 1. Although most of the patients had a good PS, of 0 or 1, at baseline, 19 (0.5%) patients had a PS of 3 or 4. The median age of the patients was 63 years, ranging from 18 to 92 years; 2.7% of the patients were 80 years or older. Two-thirds of the patients had a history of prior gastrectomy, and approximately 60% of the patients had received prior chemotherapy, mostly consisting of fluorouracil-based regimens. There were 2778 (73%), 909 (24%), and 121 (3%) patients in the appropriate, careful-use, and inappropriate groups, respectively.

The proportions of patients who were administered at the approved standard doses were: 80 mg/day for 90.5% of the patients with BSA less than 1.25 m^2; 100 mg/day for 79.1% of the patients with BSA of 1.25–1.5 m^2, and 120 mg/day for 65.8% of the patients with BSA more than 1.5 m^2. Most of the remaining patients were treated at reduced doses, usually one dose level down. The total number of courses administered ranged from 1 to 22, with the median being 2; 1020 (26.8%) and 1089 (28.6%) patients discontinued the treatment during the first and second courses, respectively.

Table 1. Patient characteristics

Characteristic		No. of patients
Total		3808
Sex	Male	2661
	Female	1147
Age (years)	<65	2158
	≧65	1650
	Median	63
	Range	18–92
ECOG performance status scale	0	2297
	1	1220
	2	272
	3, 4	19
Prior chemotherapy[a]	No	1542
	Yes	2253
Renal function[b] (by creatinine)	Normal	3560
	High (>ULN)	179
Initial dosage (mg·day-1)	80	675
	100	1968
	120	1074
	Others	91

ULN, upper limit of normal range
[a] 13 unknown cases were excluded
[b] 69 unknown cases were excluded

Safety profile

The incidences of all adverse events and the incidence of grade 3 or worse events during the first and second courses were 74.3% and 25.0%, respectively (Table 2). Seventy-seven percent of the adverse events occurred during the first course of the treatment. Major toxicities were leukocytopenia, anorexia, and nausea/vomiting; they were generally mild, and grade 3 or 4 incidences were less than 10%. Grade 3 or 4 diarrhea was also infrequent, with an incidence of 2.0%.

Regarding the eligibility status at baseline, the incidences of grade 3 or 4 leukopenia and neutropenia were higher in the careful-use + inappropriate groups ($P = 0.0001$; Table 3). Similar tendencies were seen for anemia, thrombocytopenia, gastrointestinal toxicities (nausea/vomiting/anorexia), and fatigue. Based on the case reports, the median time to the worst toxic events was 22 days for hematological toxicities and 15 days for diarrhea and stomatitis, with a median recovery time from these toxicities of around 2 weeks.

There were 90 (2.4%) early deaths (within 30 days of the initiation of the treatment), though these were mostly related to disease progression. Overall, 5 (0.1%) deaths were possibly related to the treatment: 2, patients died of serious thrombocytopenia causing cerebral hemorrhage and disseminated intravascular