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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).

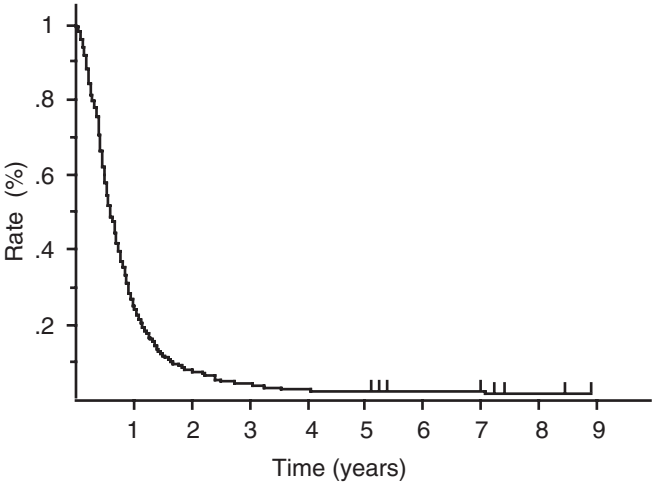

Figure 1. Overall survival of patients.

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.

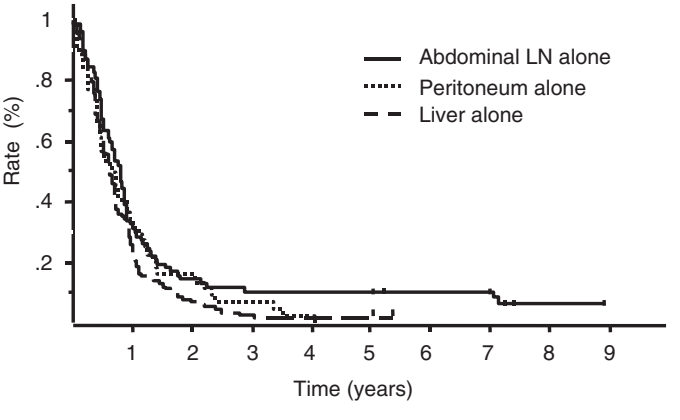

Figure 2. Survival of patients with a single metastatic site: 77 patients had a metastasis to an abdominal node, 117 had a liver metastasis and 44 had a peritoneal metastasis. LN, lymph node.

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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