C-reactive Protein is a Potential Prognostic Factor for Metastatic Gastric Cancer

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Abstract. *Background/Aim: C-reactive protein (CRP) has been associated with the development of many carcinomas, but the significance of CRP remains unclear for metastatic gastric cancer (MGC). Patients and Methods: Sixty one patients who received S-1 plus cisplatin for MGC were retrospectively identified and categorized into two groups depending on the serum CRP level before chemotherapy. Results: Overall survival was significantly shorter in the CRP≥1.0 group than in the CRP<1.0 group (median, 292 days versus 451 days; p=0.0004). Moreover, progression-free survival was significantly shorter in the CRP≥1.0 group than in the CRP<1.0 group (median, 115 days versus 188 days; p=0.0010). In a multivariate analysis, serum CRP level before chemotherapy was an independent prognostic factor for MGC (hazard ratio 4.20 [95% CI, 1.66 to 10.64] p=0.002). Conclusion: Serum CRP level before chemotherapy might be a potential prognostic factor for MGC.*

Gastric cancer is the sixth most common malignancy and the third leading cause of cancer death in the world (1). Although several novel chemotherapeutic agents, such as S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine and potassium oxonate), irinotecan, oxaliplatin and taxanes have been shown to be effective against metastatic gastric cancer (MGC), the prognosis of patients with MGC remains poor. Fluoropyrimidine plus cisplatin (CDDP) is generally considered as the standard chemotherapy for MGC worldwide and this combination has been used as a control arm in many Phase III clinical trials (2, 3). In a Phase III clinical trial in patients with MGC conducted in Japan, S-1 plus CDDP was recognized as the standard chemotherapy (4).

C-reactive protein (CRP) is produced by hepatocytes and is a marker for inflammation caused by infection and trauma. Recently, the causal relationship between inflammation, innate immunity, and cancer has been more widely accepted (5), and a previous study showed that inflammation was significantly associated with cancer death (6). It has been reported that patients with a high level of pre-diagnostic CRP subsequently showed increased colorectal cancer development (7). CRP is considered to be related to cancer progression, and increased serum levels of CRP have been detected in many carcinomas, such as colorectal (8), lung (9) and gastric cancer (10-12). Moreover, previous studies have reported that CRP level is associated with wall invasion and lymph node and distant metastasis in patients with gastric cancer (10, 11). Additionally, elevated CRP levels are associated with poor survival in many malignant tumors, such as soft tissue sarcoma, prostate cancer, breast cancer, renal cell carcinoma, colorectal cancer, non-small-cell lung cancer, malignant lymphoma, and pancreatic cancer (10, 13-20). Although it has been reported that CRP is a diagnostic indicator, a predictive factor for invasion and metastasis, and a prognostic factor in operable gastric cancer (10, 11, 21, 22), the significance of CRP for the prognosis of patients with MGC receiving chemotherapy is unclear. Since, to the best of our knowledge, no data have been reported on the subject.

Therefore, the present study assessed the relationship between CRP and the antitumor effects of S-1 plus CDDP chemotherapy in patients with MGC.

Patients and Methods

Patients. Patients with MGC who had received S-1 plus CDDP as first-line chemotherapy from January 2006 to December 2010 at Nagoya City University Hospital and Nagoya Daini Red Cross Hospital were identified through the computerized database at each institution. Patients who had discontinued chemotherapy before

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Key Words: Chemotherapy, C-reactive protein, gastric cancer, prognostic factor, CDDP, S-1.

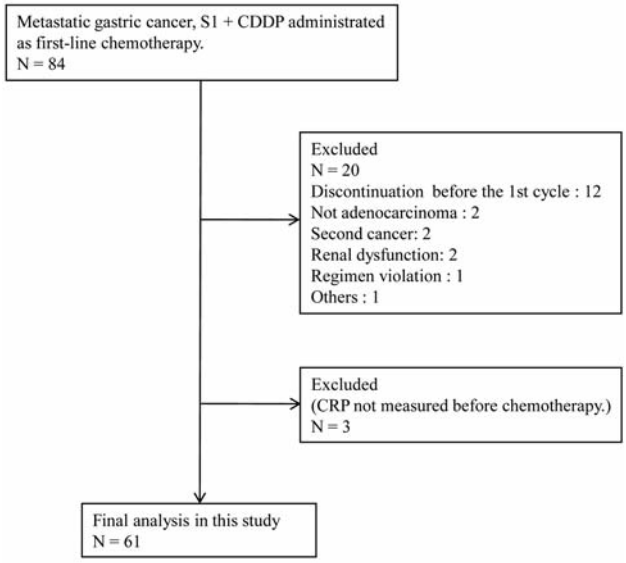

Figure 1. *Patient flow chart. S-1: tegafur, 5-chloro-2,4-dihydropyrimidine and potassium oxonate; CDDP: cisplatin.*

Table I. *Patient characteristics.*

		CRP<1.0 (n=39)	CRP≥1.0 (n=22)	*p*
Gender	Male	26	17	0.284
	Female	13	5	
Age (years)	Median	67	69	0.206
	(Range)	(32-79)	(48-79)	
Performance status	0/1/2	22/16/1	5/15/2	0.032
Histological type	Intestinal	13	10	0.348
	Diffuse	26	12	
Disease status	Advanced	34	20	0.505
	Recurrent	5	2	
Primary tumor	Resected	10	4	0.370
	Non-resected	29	18	
Site of metastases	Lymph node	22	16	0.656
	Liver	12	13	
	Lung	3	1	
	Peritoneum	17	8	
	Bone	1	2	
	Ovary	3	2	
No. of metastatic sites	1/2/≥3	26/9/4	9/7/6	0.104
Target lesions	Yes	32	20	0.295
	No	7	2	
No. of regimens	1/2/≥3	13/10/16	8/10/4	0.138

CRP: C-reactive protein.

completion of the first cycle, those with renal dysfunction (creatinine levels ≥1.3 mg/dl), those with an additional malignant tumor, those who were treated with a schedule of S-1 plus CDDP for which efficacy had not been proven, and those in whom CRP was not measured before chemotherapy were excluded from the study.

The data were retrospectively analyzed and informed consent was provided by all patients.

Out of the 84 patients with MGC who received S-1 plus CDDP as first-line chemotherapy, 23 were excluded leaving 61 patients to be evaluated for this study (Figure 1). These patients were categorized into two groups depending on the serum CRP level before chemotherapy. The following standard serum CRP values are generally accepted in relation to inflammation: CRP<0.3 mg/dl, negative; 0.3 mg/dl≤CRP<1.0 mg/dl, slightly positive; 1.0 mg/dl ≤CRP<10.0 mg/dl, moderately positive; 10.0 mg/dl≤CRP, severely positive. CRP≥1.0 mg/dl, which is clinically judged as a clear positive level, was defined as the positive group of CRP in this study. The baseline characteristics of both groups are shown in Table I.

Chemotherapy schedule. S-1 was administered orally; the dosage was based on the body surface area (BSA) of the patient: BSA <1.25 m^2, 80 mg; 1.25 m^2≤BSA<1.5 m^2, 100 mg; and BSA≥1.5 m^2, 120 mg. For the S1 plus CDDP regimen, S-1 was orally administered at the above dosage for the first 3 consecutive weeks of a 5-week cycle and 60 mg/m^2 of CDDP was administered intravenously on day 8 of each cycle (4).

Measurements. Serum CRP levels were measured within the 7 days before S-1 plus CDDP chemotherapy. The overall survival time was measured from the first day of chemotherapy until death or the last day of the follow-up period. Progression-free survival (PFS) was defined as the time from the first day of chemotherapy to disease progression, death, or the last day of follow up (whichever occurred first). Response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, Version 1.1 (23) using computed tomography (CT). In all the patients, CT evaluations were performed every 2 to 3 cycles. Performance status (PS) and toxicities were graded according to the Eastern Cooperative Oncology Group (ECOG) PS (24) and Common Terminology Criteria for Adverse Events (CTCAE ver. 4.0) (25), respectively.

Statistics. Kaplan-Meier curves were constructed in order to analyze the survival data and PFS, and differences between the two groups were compared with a log-rank test. A multivariate analysis was performed using a Cox proportional hazards model and each hazard ratio (HR) for the various prognostic factors was calculated. The other data were analyzed using a Chi-square test, Fisher's exact probability test or a Mann-Whitney *U*-test, as appropriate. *P*-values less than 0.05 were considered statistically significant. Data analyses were performed using Dr. SPSS II for Windows release 11.0.1J software (SPSS Japan, Tokyo, Japan).

Results

Patients. Thirty nine patients were included in the CRP<1.0 group and 22 patients were included in the CRP≥1.0 group. Most of the patients in the CRP<1.0 group had a PS of 0 (56%), while the majority of the patients in the CRP≥1.0 group had a PS of 1 (68%). The CRP≥1.0 group had a significantly greater percentage of patients with a PS of 1 or 2 (77%) compared to the CRP<1.0 group (44%) (p=0.011)

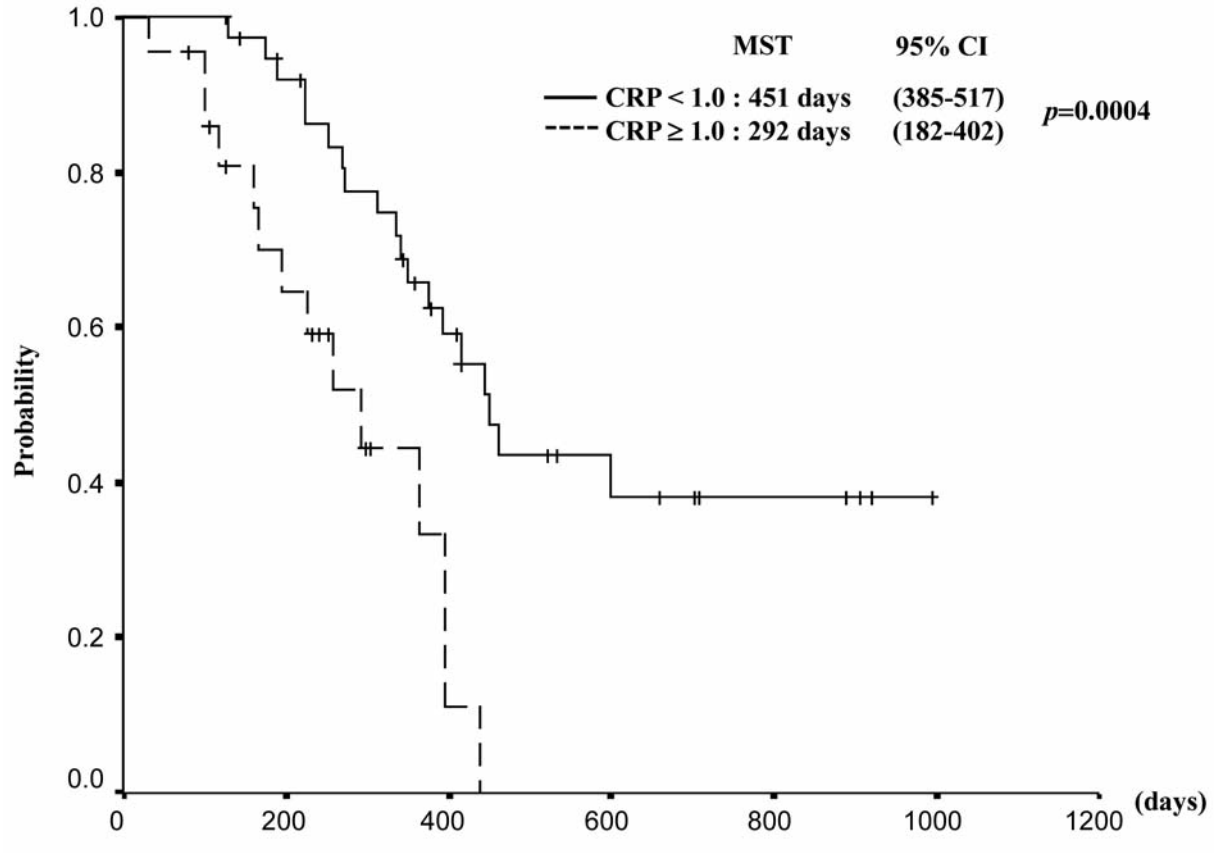

Figure 2. *Overall survival. MST: median survival time; 95% CI: 95% confidence interval.*

(Table I). There were no significant differences between the groups for any of the other patient characteristics.

Overall survival. The median survival time (MST) for the overall population was 394 days (95% confidence interval [CI], 336 to 452). The median overall survival was significantly shorter in the CRP≥1.0 group than in the CRP<1.0 group (292 days [95% CI, 182 to 402] *versus* 451 days [95% CI, 385 to 517]; p=0.0004) (Figure 2).

Progression-free survival. The median PFS for the overall population was 171 days (95% CI, 147 to 195). The median PFS was significantly shorter in the CRP≥1.0 group than in the CRP<1.0 group (115 days [95% CI, 89 to 141] *versus* 188 days [95% CI, 118 to 258]; p=0.0010) (Figure 3).

Overall response. The response rate was determined in 52 patients with target lesions, no significant differences were noted between the CRP<1.0 group and the CRP≥1.0 group (Table II).

Table II. *Response rate*.

	Target lesion							
	(+)	(–)	CR	PR	SD	PD	RR (%)	*p*
CRP<1.0	32	7	0	10	14	8	31.3	0.924
CRP≥1.0	20	2	0	6	6	8	30.0	
Total	52	9	0	16	20	16	30.8	

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RR: response rate; CRP: C-reactive protein.

Adverse events. The hematological adverse events, greater than grade 3 were leukopenia (7.7%, 0%), neutropenia (23.1%, 4.5%) and anemia (7.7%, 27.3%) in the CRP<1.0 and the CRP≥1.0 groups, respectively (Table III). Anemia occurred significantly more frequently in the CRP≥1.0 group (27.3%) than in the CRP<1.0 group (7.7%). Although no significant differences were noted, there were more incidences of leukopenia and neutropenia in the CRP<1.0 group compared to the CRP≥1.0 group.

Prognostic factors in univariate and multivariate analyses. Some factors that influence overall survival were analyzed

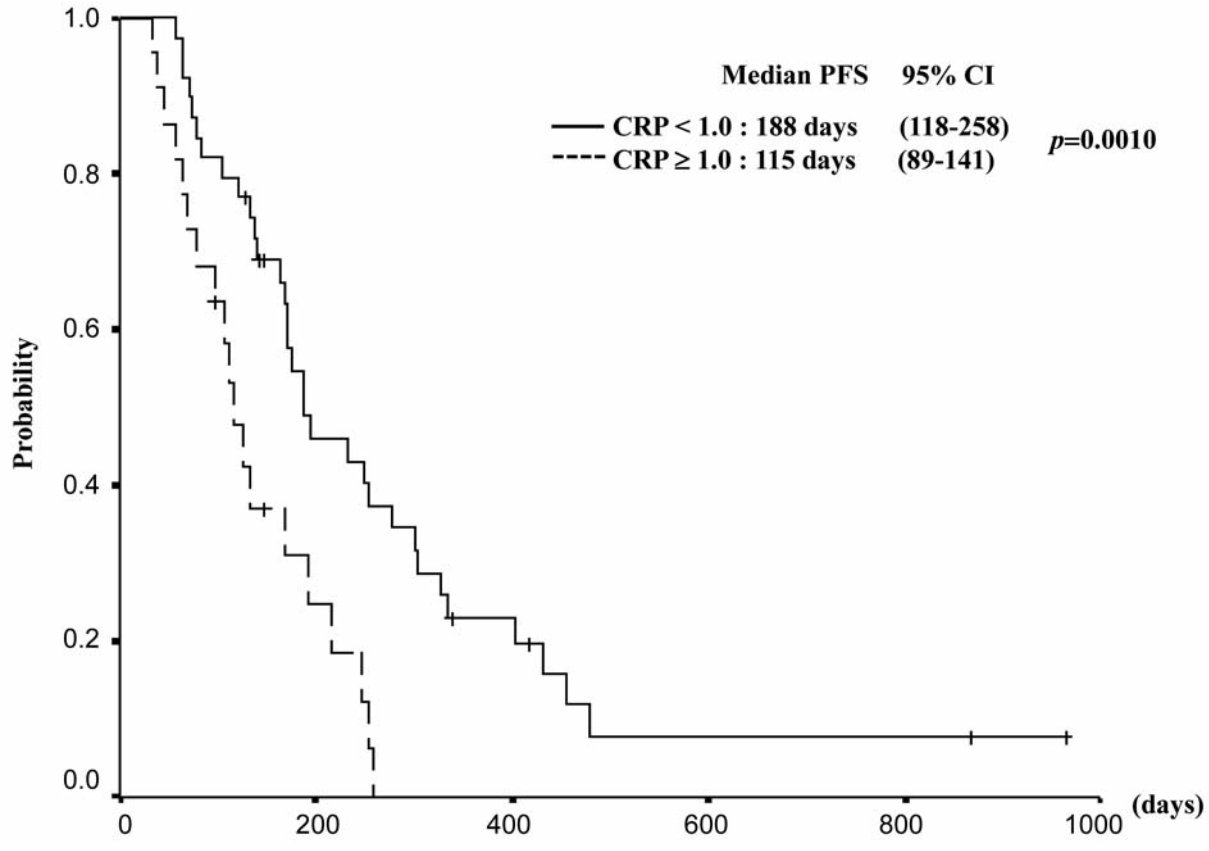

Figure 3. *Progression-free survival. PFS: progression-free survival; 95% CI: 95% confidence interval.*

and are shown in Table IV. Serum CRP (p=0.0004) and gender (p=0.0466) were extracted as prognostic factors in the univariate analysis. Moreover, a multivariate analysis was performed using four factors (CRP, gender, PS and the presence of a primary tumor) which were all p<0.1 in univariate analysis. Multivariate analysis showed that CRP ≥1.0 mg/dl and female were independent poor prognostic factors.

Discussion

The present study revealed that CRP is an independent prognostic factor for patients with MGC.

In order to remove bias by treatment, only patients who received S-1 plus CDDP for MGC as first-line chemotherapy were included in this study. MST and median PFS were 394 and 171 days, respectively, which were consistent with the data in a previous Phase III trial (MST: 390 days, median PFS: 180 days) (4), suggesting that the present data were reliable.

Although no significant differences were found for response rate in this study, the CRP≥1.0 group showed significantly shorter PFS and poorer overall survival than the CRP<1.0 group. These results suggested that chemosensitivity declines quickly even if anticancer agents are effective temporarily in the CRP≥1.0 group. CRP is produced as a response to some inflammatory cytokines and has been widely accepted as a

Table III. *Adverse events ≥Grade 3.*

	CRP<1.0 (n=39) N (%)	CRP≥1.0 (n=22) N (%)	*p*
Hematological			
Leukopenia	3 (7.7)	0 (0)	0.254
Neutropenia	9 (23.1)	1 (4.5)	0.059
Anemia	3 (7.7)	6 (27.3)	0.047
Thorombocytopenia	2(5.1)	1 (4.5)	0.707
Febrile neutropenia	1 (2.6)	0 (0)	0.639
Non-hematological			
Fatigue	1(2.6)	2 (9.1)	0.293
Nausea	3 (7.7)	1 (4.5)	0.543
Vomiting	1 (2.6)	0 (0)	0.639
Anorexia	5 (12.3)	2 (9.1)	0.505
Acute coronary syndrome	0 (0)	1 (4.5)	0.361
Hearing impairment	1 (2.6)	0 (1.6)	0.639

CRP: C-reactive protein.

Table IV. *Univariate and multivariate analyses for survival.*

	MST (95% CI) (days)	Univariate analysis	Multivariate analysis	
		p	HR (95% CI)	*p*
CRP				
<1.0	451 (385-517)	0.0004	1	0.002
≥1.0	292 (182-402)		4.20 (1.66-10.64)	
Gender				
Male	451 (227-675)	0.0466	1	0.010
Female	341 (234-448)		2.62 (1.26-5.49)	
Age (years)				
<65	392 (317-467)	0.8784		
≥65	394 (323-465)			
PS				
0	451 (222-680)	0.0897	1	0.855
1 or 2	341 (238-444)		0.92 (0.38-2.25)	
Histological type				
Intestinal	394 (350-438)	0.7358		
Diffuse	365 (250-480)			
Primary tumor				
Resected	451 (430-472)	0.0667	1	0.104
Non-resected	365 (284-446)		2.14 (0.85-5.35)	
Peritoneal metastasis				
(+)	394 (369-419)	0.7742		
(–)	437 (294-580)			
Metastatic sites				
1	416 (344-488)	0.5052		
≥2	335 (246-424)			
Target lesion				
(+)	392 (345-439)	0.7204		
(–)	445 (74-816)			

MST: Median survival time; CI: confidence interval; HR: hazard ratio; CRP: C-reactive protein; PS: performance status.

representative marker for inflammation. Inflammatory cells have powerful effects on tumor development by releasing growth and survival factors, promoting angiogenesis and lymphangiogenesis, stimulating DNA damage, and remodeling the extracellular matrix invasion (5). Hence, higher levels of inflammatory cytokines and chemokines were hypothesized to result in poor survival for patients with MGC in the CRP≥1.0 group. In fact, some previous reports have shown positive correlation between levels of serum CRP and interleukin-6 (IL-6), one of the inflammatory cytokines in gastric cancer (10, 11).

Although there were significantly more patients with PS≥1 in the CRP≥1.0 group *versus* the CRP<1.0 group in this study, CRP was the strongest prognostic factor in the multivariate analysis that included PS. PS≥2 has been previously identified as a poor prognostic factor in a study of patients with advanced gastric cancer treated with capecitabine plus cisplatin (26) and a large study of patients with advanced and metastatic esophagogastric cancer (27). However, no study investigated CRP. Due to the small number of patients with PS≥2, this population could not be included in the present analysis. However, considering that the CRP≥1.0 group included more patients with PS≥1, the CRP level may positively correlate with PS.

Being female was the only other independent prognostic factor in the present study, but the significance is unclear. Although it is well known that the incidence of gastric cancer is higher for men than for women, previous studies reported that women with gastric cancer showed better prognosis than men (28, 29). However, as these previous studies rarely included patients with MGC, there may be some differences between localized gastric cancer and MGC.

The frequency of leukopenia and neutropenia was comparatively reduced, whereas anemia was comparatively increased in the CRP≥1.0 group. The white blood cell and neutrophil counts may have increased prior to chemotherapy due to inflammation in the CRP≥1.0 group. Similarly, some anemia may have already occurred due to inflammation in the CRP≥1.0 group. These adverse events can be speculated to be due to baseline differences between the two groups.

The current study had potential limitations due to its retrospective nature and small sample size. However, we believe the results are reliable because the population was restricted to the same first-line chemotherapy and prominent differences for survival were observed between the two groups in the multivariate analysis. Therefore, the results provide important information on the management of MGC. CRP is considered to be a very good and useful prognostic factor because measurement of CRP levels is easy, cost effective and familiar to most physicians.

In conclusion, serum CRP levels before treatment might be a potential prognostic factor for patients with MGC. As early progression of MGC is predicted for patients with high CRP levels, more stringent follow-up should be expected for this group.

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Received November 21, 2011
Revised December 18, 2011
Accepted December 21, 2011