C-Reactive Protein Is a Negative Independent Factor in Patients with Stage IV Colorectal Cancer Undergoing Oxaliplatin-based Chemotherapy

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Abstract. *Background/Aim: To determine the clinical significance of C-reactive protein (CRP) concentration in patients with stage IV colorectal cancer (CRC) undergoing oxaliplatin-based chemotherapy. Patients and Methods: We retrospectively reviewed the medical charts of 112 patients with stage IV CRC who had received modified FOLFOX6 (5-fluorouracil, oxaliplatin, leucovorin) between January 2006, and December 2010 and used Cox's proportional hazard model to determine for independent prognostic factors of survival. We generated receiver operating characteristics (ROC) curves to determine the optimal cut-off for the discrimination of the duration of survival by CRP concentration. Results: According to the multivariate analysis, increased CRP concentration (p=0.04) and non-curative surgery (p<0.01) were independent unfavorable factors for survival, and the optimal cut-off CRP concentration according to dichotomized duration of survival (3–24 months) ranged from 0.8 to 1.2 mg/dl. Conclusion: Pre-chemotherapy CRP concentrations may be useful for predicting survival of patients with stage IV CRC.*

In absence of a reliable way to predict survival of patients with cancer undergoing chemotherapy, there is continuous interest in identifying prognostic factors that allow fir a more accurate patient stratification and which will contribute to rational study design and analysis (1, 2).

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The presence of a systemic inflammatory response, as evidenced by increased concentrations of circulating serum C-reactive protein (CRP), is associated with poor survival in patients with colorectal cancer (CRC) who have undergone curative resection (3-7). These responses are thought to be due to infiltration of proinflammatory lymphocytes, cytokines and chemokines into the tumor microenvironment, which predisposes the tumor for further progression, invasion and metastasis (8).

Few studies have investigated the relationship between serum (plasma) CRP concentration and survival in patients with stage IV or recurrent CRC (9-12). In addition, the optimal cut-off for discrimination of the duration of survival in patients with such advanced disease by serum CRP concentration has not yet been determined as far as we know. To address these issues, we undertook a retrospective study of patients with stage IV CRC who had undergone oxaliplatin-based chemotherapy (OBC).

Patients and Methods

This study was approved by the Ethics Committee of Saitama Medical Center, Saitama Medical University.

Patients. We reviewed the medical charts of 112 patients with stage IV CRC who had undergone OBC between January 2006 and December 2010 in the Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University. During this study period, the regimen of first-line OBC for patients with unresectable stage IV CRC was modified FOLFOX6 (5-fluorouracil, oxaliplatin, leucovorin; median number of cycles, 11; range=1-49) with bevacizumab whenever possible. Modified FOLFOX6 without the addition of bevacizumab was also administered to patients with stage IV CRC after resection of the primary tumor and synchronous metastasectomy (R0 resection), even though such therapy is challenging and not evidence-based. No patient had any clinical evidence of infection or any other inflammatory condition at the commencement of chemotherapy.

Table I. *Univariate and multivariate analysis in relation to overall survival.*

	Univariate		Multivariate	
Variables	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Age;years				
<70 (n=72)	1			
≥70 (n=40)	1.267 (0.823-1.951)	0.2832		
Gender				
Male (n=70)	1			
Female (n=42)	1.039 (0.679-1.588)	0.8612		
Performance status				
0 (n=59)	1			
1, 2 (n=53)	1.862 (1.218-2.845)	0.0041	1.454 (0.868-2.437)	0.1551
Tumor site				
Colon (n=94)	1.167 (0.676-1.995)	0.5871		
Rectum (n=18)	1			
Tumor differentiation				
Well/moderate (n=90)	1			
Poor/others (n=22)	1.625 (0.512-4.374)	0.3348		
No. metastatic organ				
1 (n=62)	1			
2, 3 (n=50)	1.463 (0.966-2.216)	0.0724	1.414 (0.853-2.346)	0.1795
Surgery				
R0 resection (n=14) 1				
Other (n=98)	4.589 (1.857-11.34)	0.0010	3.554 (1.356-9.313)	0.0099
CRP	1.086 (1.023-1.153)	0.0069	1.083 (1.000-1.169)	0.0426
Albumin	0.616 (0.437-0.868)	0.0057	1.085(0.662-1.778)	0.7464
ALP	1.001 (1.000-1.001)	0.0474	1.000 (0.999-1.001)	0.7796
LDH	1.001 (1.000-1.001)	0.6911		
WBC	1.000 (1.000-1.000)	0.4963		
Hb	0.813 (0.694-0.950)	0.0092	0.862 (0.712-1.045)	0.1302
CEA	1.000 (1.000-1.000)	0.8653		
CA19-9	1.000 (1.000-1.000)	0.0673	1.000 (1.000-1.000)	0.3816

CI: Confidence interval; well/moderately: well- or moderately-differentiated adenocarcinoma; poor: poorly-differentiated adenocarcinoma; CRP: C-reactive protein; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; WBC: white blood cell count; Hb: hemoglobin; CEA; carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Evaluated factors. Clinicopathological, surgical and laboratory variables were retrieved from patients' charts. The clinicopathological factors included age, sex, performance status (PS) before chemotherapy, site of primary tumor, degree of cellular differentiation, and number of organ affected by metastases. The surgical factors included performance of primary tumor resection or stoma creation and curative intent (R0 resection or non-curative resection). The laboratory data included hemoglobin (Hb) concentration, white blood cell count (WBC), and serum concentrations of CRP, albumin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA; cut-off, 6.7 ng/ml), and carbohydrate antigen 19-9 (CA19-9; cut-off, 37 U/ml).

Survival time was calculated from the start of chemotherapy to death from any cause, or was censored when patients were alive at the last follow-up.

Statistical analysis. All data were analyzed using with a statistical software program (Statflex, ver6.0; Artec, Osaka, Japan). Grouping of categorical and continuous variables was carried out using standard thresholds. Cox proportional hazard regression analysis was used to determine independent significant factors for survival. Factors with a *p*-value less than 0.1 according to univariate analysis were assessed by multivariate analysis. A receiver operating characteristics (ROC) curve was generated to determine the optimal cut-off as CRP concentration according to dichotomized durations of survival. *p*-Values less than 0.05 were considered statistically significant.

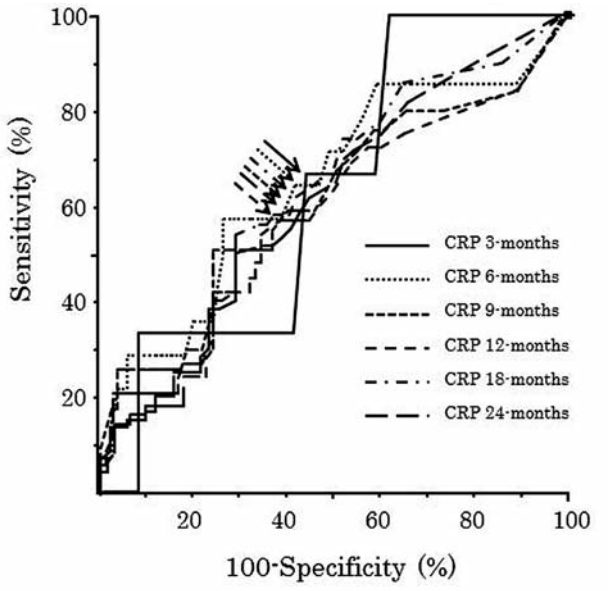
Results

Patients' characteristics. The study included 70 male and 42 female patients. The median age was 66 years (range=31-85 years). The primary site of tumor was colon in 94 patients and rectum in 18. Pre-chemotherapy surgical procedures were performed in 99 patients (88%). The types of surgery included primary tumor resection for palliation in 69 patients, primary tumor resection and metastasectomy (R0 resection) in 14, and stoma creation in 16.

Cox proportional regression analysis. Univariate analysis, which was performed for age (<70 *vs.* ≥70 years), sex (male

vs. female), PS (0/1 *vs*. 2), tumor site (colon *vs*. rectum), number of metastatically involved organ (1/2 *vs*. 3), curability (R0 resection *vs*. others), CRP, albumin, ALP, LDH, WBC, Hb, CEA and CA19-9 concentrations, showed that higher PS ($p<0.01$), greater number of metastatically involved organ ($p=0.07$), curability ($p<0.01$), high CRP ($p<0.01$), low albumin ($p<0.01$), high ALP ($p=0.05$), low Hb ($p<0.01$) and high CA19-9 ($p=0.07$) were associated with unfavorable survival (Table I). These factors were, therefore, subjected to multivariate analysis, which identified curability [hazard ratio (HR)=3.554 95% confidence interval (CI) (1.356-9.313), $p<0.01$] and high CRP [HR=1.083 (1.00-1.169), $p=0.04$] as significant unfavorable factors for survival (Table I).

ROC curve analysis. The optimal cut-off for serum CRP concentration according to various dichotomized survival periods (3, 6, 9, 12, 18, and 24 months) with the area under the curve (AUC) and sensitivity, specificity, accuracy for each cut-off CRP concentration are shown in Figure 1. The optimal cut-offs ranged from 0.8 to 1.2 mg/dl according to the dichotomized survival periods. The cut-off with the highest AUC (0.64) was 1.2 mg/dl for 3-month survival. The sensitivity, specificity, and accuracy for prediction of survival at three months by this concentration were 66.7% 43.1%, and 57.1%, respectively.



Survival period (months)	AUC	Cut-off value (mg/dl)	Sensitivity (%)	Specificity (%)	Accuracy (%)
3-months	0.639	1.23	66.7	43.1	57.1
6-months	0.654	1.25	64.3	40.8	57.1
9-months	0.610	1.07	58.3	43.2	57.1
12-months	0.593	0.97	57.6	44.3	55.4
18-months	0.622	0.87	62.0	41.9	59.8
24-months	0.615	0.81	58.3	42.3	58.0

CRP 3-months cut off point (⟵), CRP 6-months cut off point (⟵), CRP 9-months cut off point (⟵), CRP 12-months cut off point (⟵), CRP 18-months cut off point (⟵), CRP 24-months cut off point (⟵)

Figure 1. *Receiver operating characteristics curves (ROC) for optimal cut-off C-reactive protein (CRP) concentrations for 112 patients with patients with stage IV colorectal cancer (CRC) undergoing oxaliplatin-based chemotherapy according to various survival durations of survival. AUC: Area under the ROC curve.*

Discussion

We have clearly shown that an increased CRP concentration is an independent prognostic factor for unfavorable survival in patients with stage IV CRC undergoing OBC, and that the optimal cut-off ranges from 0.8 to 1.2 mg/dl according to dichotomized durations of survival (3-24 months).

Increased CRP concentration is a negative independent prognostic factor in patients with stage IV CRC undergoing chemotherapy and has not previously been reported, as far as we know. Ishizuka *et al*. have reported that CRP is an independent factor for postoperative survival in patients with synchronous or metachronous liver metastasis from CRC (11). In their study, the cut-off concentration (1.0 mg/dl) was based on the Glasgow prognostic score (GPS), an inflammation-based prognostic score that includes both CRP and albumin concentrations that has been studied by previous investigators (13, 14). In most previous studies, the cut-off concentrations for relationships between CRP concentration and survival in patients with CRC, which range from 0.5 to 1.0 mg/dl, seem to have been set either according to GPS or the lower limit of detection of CRP (3-6, 9-12). However, Toiyama *et al*. subjected their findings to ROC analysis such as in our study and calculated a cut-off of 0.5 mg/dl for CRP concentration; they reported CRP to be an independent predictor of postoperative survival in patients with stage I-III CRC (7).

Our ROC analysis for optimal cut-offs for CRP concentrations showed a tendency towards an inverse relationship between the selected survival period (months) and CRP concentration. The cut-off concentrations all fell within the limited range of 0.8-1.2 mg/dl. Although the cut-off CRP concentration for predicting survival in patients with metastatic CRC undergoing chemotherapy requires further investigation, our findings suggest that it is appropriate for it to be set at approximately 1.0 mg/dl.

McMillan *et al*. have reported that the GPS is a useful predictor of postoperative survival in patients with CRC (15). Recent reports evaluating the utility of the GPS for patients with all stages of CRC have confirmed that the GPS is a useful predictor of survival (12, 16). Some studies have

reported that a modified GPS is superior to the original GPS for predicting survival in patients with CRC (17-19). Ishizuka *et al*. reported that this modified GPS is an important and independent predictor of survival in patients with metastatic CRC undergoing modern chemotherapy such as FOLFOX or FOLFIRI, but that CRP or albumin alone are not (10). In our study, albumin was a significant predictor for survival according to univariate analysis, but not according to multivariate analysis. Because CRP and albumin concentrations were inversely correlated (data not shown) in our study, CRP alone might be a sufficient independent predictor of survival in patients with stage IV CRC undergoing OBC.

In agreement with a previous study (20), we also found that non-curative surgery is an independent unfavorable predictor of survival. According to multivariate analysis in our study, OBC after R0 resection appears to improve prognosis; however, such chemotherapy is not evidence-based. Nevertheless, several retrospective studies have demonstrated favorable outcome for OBC after resection of synchronous or metachronous liver metastases from CRC (21, 22).

CRP concentration is easier and less expensive to measure than conventional tumor markers such, as CEA and CA19-9 (11) or complex and expensive techniques such as computed tomography, magnetic resonance imaging and positron emission-tomography. CRP concentrations could readily be routinely measured in follow-up blood chemistry examinations on outpatients or at times of admission, and assessed in the light of optimal cut-off points to improve overall survival rate of patients with CRC.

Although this was a retrospective study with a small sample size, it did establish that measurement of CRP concentration is a simple and convenient means of predicting prognosis of patients with stage IV CRC undergoing OBC. A prospective study with a larger series of cases is needed to confirm our findings.

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