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Elevated Serum C-Reactive Protein as a Prognostic Marker in Small Cell Lung Cancer

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Purpose: Elevated C-reactive protein (CRP) is associated with poor prognosis in several tumor types. The purpose of this study was to investigate serum CRP as a prognostic marker in small cell lung cancer (SCLC). **Materials and Methods:** The pretreatment serum CRP level was measured in 157 newly diagnosed SCLC patients, and correlation between serum CRP level and other clinical parameters was analyzed. Multivariate analyses were performed to find prognostic markers using Cox's proportional hazards model. **Results:** The initial CRP concentration was within the normal range in 72 (45.9%) patients and elevated in 85 (54.1%) patients. There was a significant correlation between serum CRP level and the extent of disease (p<0.001), weight loss (p=0.029) and chest radiation (p=0.001). Median overall survival (OS) in the normal CRP group was significantly longer than with the high CRP group (22.5 months vs. 11.2 months, p<0.001). Extent of disease (p<0.001), age (p=0.025), and performance status (p<0.001) were additional prognostic factors on univariate analysis. On multivariate analysis, elevated serum CRP level was an independent prognostic factor for poor survival (HR=1.8; p=0.014), regardless of the extent of disease (HR=3.7; p<0.001) and performance status (HR=2.2; p<0.001). **Conclusion:** High level of CRP was an independent poor prognostic serum marker in addition to previously well-known prognosticators in patients with SCLC.

Key Words: C-reactive protein, prognosis, small cell lung cancer

INTRODUCTION

Small cell lung cancer (SCLC), which accounts for 20-25% of all lung cancers, is highly sensitive to radiotherapy and chemotherapy. Traditionally, well-known prognostic factors of SCLC include extent of disease, performance status, and weight loss. Several laboratory factors, such as neuron-specific enolase (NSE), cytokeratin-19 fragments (CYFRA 21-1), carcinoembryonic antigen, lactate dehydrogenase (LDH), and albumin have been studied to show additional independent prognostic value, however, the weights of their values are still controversial and require prospective validation.[1]

There have been numerous reports about the relationship between chronic inflammation and cancer. The inflammatory cells and cytokines found in tumor highly like-

ly to contribute to tumor growth, progression, and immunesuppression compared to cope with an effective host antitumor response.[2-4] In fact, about 15% of cancers are initiated by chronic inflammation or infection such as helicobacter pylori, hepatitis virus, Epstein-Barr virus, and other bacteria. Persistent infection of the host induces chronic inflammation, and inflammatory cells induce DNA damage in proliferating cell, by generating reactive oxygen and nitrogen species.[3] Furthermore, it is well demonstrated by laboratory research that pro-inflammatory cytokines could promote tumor growth and metastasis by altering tumor cell biology and activating stromal cells in the tumor microenvironment.[3,5,6]

C-reactive protein (CRP) is a nonspecific serum marker of acute-phase inflammatory response, and it is produced by hepatocytes which are regulated by interleukin (IL)-6.[4,7] Several possible mechanisms have been postulated for the relationship between CRP and cancers; first, tumor growth can cause tissue inflammation, hence increasing CRP level. Second, CRP could be an indicator of an immune response to tumor antigens. Third, cancer cells could increase the production of inflammatory cytokines, which could induce high CRP concentration in cancer patients.[4] Many studies showed the elevation of pretreatment CRP to be a significant prognostic parameter in patients with esophageal cancer,[8-10] hepatocellular carcinoma,[11] colorectal cancer,[12-14] renal cell cancer,[15-17] ovarian cancer,[18] and non-small cell lung cancer (NSCLC).[19-23] Furthermore, we recently reported an association between preoperative serum CRP levels and pathologic parameter such as tumor size and lymphovascular invasion in patients with NSCLC.[24]

At present, little is known about the relevance of inflammatory markers to survival in SCLC. In this study, we evaluated the relationship between CRP and SCLC, and investigated CRP as a potential prognostic serum marker in patients with SCLC.

MATERIALS AND METHODS

We reviewed patients who had histologically confirmed SCLC and received chemotherapy at the Yonsei Cancer Center, Seoul, Korea. Retrospective analysis was performed regarding initial serum CRP concentration, age, gender, extent of disease, weight loss, Eastern Cooperative Oncology Group (ECOG) performance status at first presentation, smoking history, co-morbidity, best response to chemotherapy, and survival. Patients with active concurrent infection were excluded. All patients received platinum-based combination chemotherapy, mostly with irinotecan or etoposide. Patients with limited disease underwent concurrent chemoradiation therapy including 5,400 cGy of thoracic radiation. Traditionally, the two-stage system of the Veteran's Administration Lung Group was used to classify the patients. Limited disease is defined as disease confined to the ipsilateral chest within a single radiation field, and extensive disease was defined as disease beyond the ipsilateral hemithorax including malignant pleural or pericardial effusion or hematogenous metastasis. Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are classified as limited-stage, while contralateral hilar and supraclavicular lymphadenopathy are usually classified as extensive stage disease.[25] Weight loss was recorded in kilograms (kg) and defined as more than 5 kg or 10% of baseline body weight loss during the past six months. Co-morbidity included the following conditions; hypertension, diabetes mellitus, cerebrovascular disease, ischemic heart disease, asthma, chronic obstructive lung disease, liver cirrhosis, and end stage renal disease. Response Evaluation was performed with CT scan every two cycles, according to the Response Evaluation Criteria in Solid Tumors guidelines.[26]

Pretreatment CRP values were measured from peripheral venous blood samples as part of the clinical routine, using an automatic nephelometer (Beckman Coulter image, Fullerton, CA, USA), according to the manufacturer's instructions. Normal serum level was defined as ≤0.8 mg/dL by manufacturer's manual. The correlation between serum CRP level and other categorical clinical variables was compared by Pearson's chi-square test. Overall survival (OS) was measured from the date of diagnosis until the date of death or final follow up. Progression-free survival (PFS) was defined as the time from the date of diagnosis until the date of tumor progression or death. The survival data were estimated using Kaplan-Meier curve and compared using the log-rank test. Multivariate analyses were performed to find prognostic markers using Cox's proportional hazards model. A *p*-value of less than 0.05 was considered to be statistically significant. The study was approved by our institutional review board.

RESULTS

Patients

A total of 157 patients were included in this study. Patient characteristics are summarized in Table 1. Fifty-nine pa-

tients (37.6%) had limited disease and 98 patients (62.4%) had extensive disease. The median age was 65 years (range, 46-82), and majority of patients were male (n=140; 89.2%). Most of the patients (n=127; 79%) had good performance status (ECOG 0-1), and only 29 patients (18.5%) had significant weight loss. Ten patients (6.4%) had never smoked. All patients included in this study underwent platinum-based chemotherapy in combination with irinotecan (63.1%), etoposide (31.8%), or other agents (5.1%) according to physicians' choice.

Serum CRP and patient characteristics

The initial CRP concentration in 72 patients (45.9%) was within the normal range, and elevated in 85 patients (54.1%).

Table 1. Baseline Characteristics

Characteristics	Overall (%) (n=157)	Serum CRP		
		Normal (n=72)	Elevated (n=85)	*p* value*
Stage				
Limited	59 (37.6)	39 (54.2)	20 (23.5)	<0.001
Extensive	98 (62.4)	33 (45.8)	65 (76.5)	
Age, median (range)	65 (46-82)			
<65	72 (45.9)	32 (44.4)	40 (47.1)	0.743
≥65	85 (54.1)	40 (55.6)	45 (52.9)	
Gender				
Male	140 (89.2)	61 (84.7)	79 (92.9)	0.099
Female	17 (10.8)	11 (15.3)	6 (7.1)	
Performance status				
ECOG 0-1	124 (79)	60 (83.3)	64 (75.3)	0.218
ECOG 2	33 (21)	12 (16.7)	21 (24.7)	
Weight loss				
No	128 (81.5)	64 (88.9)	64 (75.3)	0.029
Yes	29 (18.5)	8 (11.1)	21 (24.7)	
Smoking				
Never	10 (6.4)	7 (9.7)	3 (3.6)	0.153
Ever	146 (93.6)	65 (90.3)	81 (96.4)	
Co-morbidity†				
No	52 (33.1)	19 (26.4)	33 (38.8)	0.099
Yes	105 (66.9)	53 (73.6)	52 (61.2)	
WBC				
Normal	72 (45.9)	40 (52.6)	36 (42.4)	0.099
High	85 (54.1)	32 (44.4)	49 (57.6)	
Chemotherapy in combination with platinum‡				
Irinotecan	99 (63.1)	48 (66.7)	51 (60.1)	0.575
Etoposide	48 (30.6)	19 (26.4)	29 (34.1)	
Others§	10 (6.4)	5 (6.9)	5 (5.9)	
Chest-radiation				
No	100 (63.7)	36 (50.0)	64 (75.3)	0.001
Yes	57 (36.3)	36 (50.0)	21 (24.7)	
Treatment response				
Responder	104 (66.3)	52 (76.5)	52 (65.8)	0.157
Non-responder	33 (27.4)	16 (23.5)	27 (34.2)	
Non-evaluable	10 (6.3)			

ECOG, Eastern Cooperative Oncology Group; CRP, C-reactive protein; WBC, white blood cell count.
*Chi-squre test between normal CRP and elevated CRP group.
†Co-morbidity, hypertension, diabetes mellitus, cerebrovascular disease, ischemic heart disease, asthma, chronic obstructive lung disease, liver cirrhosis, and end stage renal disease (severity was not specified).
‡Platinum, cisplatin or carboplatin.
§Others, ifosfamide, topotecan, or belotecan.

The mean value of serum CRP prior to treatment was 4.7±7.6 mg/dL; 0.3±0.2 mg/dL in the normal CRP group and 8.4±8.8 mg/dL in the high CRP group. Serum CRP level was significantly associated with the extent of disease (p<0.001), chest radiation (p=0.001) and weight loss (p=0.029), but two groups of extensive disease (limited vs. extensive) and group who received chest radiation or not showed almost same composition.

Tumor response and survival

There was a trend for patients in the normal CRP group toward higher response rate to chemotherapy (76.5% vs. 65.8%; p=0.157). With a median follow-up duration of 9.3 months (range, 0.3-62.7), median PFS was 9.3 months [95% CI, 7.6-11.1], and median OS was 13.7 months (95% CI, 8.9-18.6). The median PFS and OS in the normal CRP group was significantly longer than with high CRP group (PFS, 11.0 months vs. 7.5 months; p=0.009; OS, 22.5 months vs. 11.2 months, p<0.001) (Figs. 1 and 2). Additionally, the extent of disease (23.0 months vs. 10.2 months, p<0.001), age (19.1 months vs. 12.5 months, p=0.026), performance status (18.4 months vs. 5.3 months, p<0.001), and chemo-responsiveness (22.2 months vs. 4.9 months, p<0.001) were statistically significant factors in univariate analysis (Table 2). However, weight loss was not statistically significant for survival in univariate analysis (p=0.17).

In multivariate Cox regression model (Table 3), elevated CRP level was an independent prognostic marker for poor survival (HR=1.8, 95% CI, 1.1-2.9; p=0.014), regardless of extensive disease (HR=3.7; p<0.001) and poor performance status (HR=2.2; p<0.001).

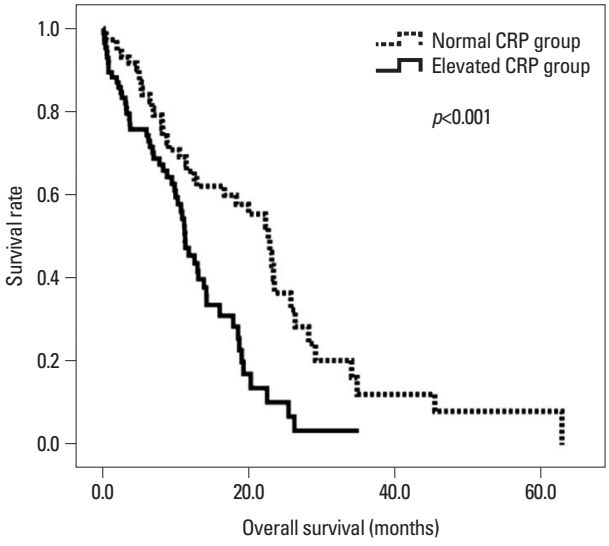

Fig. 1. Kaplan-Meier survival curve for overall survival in patients with normal CRP and elevated CRP group. CRP, C-reactive protein.

DISCUSSION

To our best knowledge, this is the first report to evaluate the clinical usefulness of serum CRP for predicting survival of SCLC patients. In the multivariate analysis, pre-treatment serum CRP was revealed as a significant prognostic marker of SCLC, together with other well-known factors, such as stage and performance status.

Table 2. Univariate Analysis of Survival

	Variables	Median survival time (95% confidence interval)	p value
Age	<65	19.133 (11.868-26.399)	0.025
	≥65	12.467 (10.386-14.547)	
Performance status	ECOG 0-1	18.400 (13.818-22.982)	<0.001
	ECOG ≥2	5.300 (1.484-9.116)	
Stage	Limited	23.000 (21.998-24.002)	<0.001
	Extensive	10.167 (8.106-12.228)	
CRP	Normal	22.533 (18.918-26.149)	<0.001
	Elevated	11.167 (9.373-12.960)	

CRP, C-reactive protein.

Table 3. Factors Independently Affecting Overall Survival

Variable	p value*	Hazard ratio (95% confidence interval)
Serum CRP	0.014	1.803 (1.129-2.877)
Performance status	<0.001	2.226 (1.427-3.474)
Extent of disease	<0.001	3.660 (1.129-2.877)

CRP, C-reactive protein.
*Multivariate analysis by Cox's regression.

In various types of malignancy, clinical decision making before treatment is generally based on established clinical and histopathologic prognosticators. The knowledge of prognostic factors, therefore, is important, so that it allows to classify patients who are candidates for newest intensive treatment. Traditionally, two-stage system, performance status, and weight loss have been key prognostic factors in SCLC patients.[1,27] Other prognostic variables, such as gender and age, have also been well-known as prognostic factors for SCLC, even though some controversies remain.[1,28] Simple biochemical tests or serum markers are also important, and numerous studies showed that NSE, CYFRA 21-1, and LDH are promising prognostic factors.[29-36]

Serum CRP levels, measurement of which is relatively inexpensive and easy to quantify in daily clinical practice, can be elevated in various acute and chronic benign conditions such as cardiovascular disease, type 2 DM, arthritis, inflammatory bowel disease, trauma, and transplant rejection.[4,24] In this study, patients with co-morbidity were 66.9% of all patients, however, we failed to observe any correlation between CRP levels and co-morbidity (Table 1). As stated above, there have been many efforts to investigate the relationship between serum CRP and prognosis in several types of cancer. In NSCLC, preoperative CRP level provided prognostic information and was associated with pathologic tumor size and lympho-vascular invasion.[21,23,24] In hepatocellular carcinoma, the correlation of preoperative CRP level with tumor size and portal vein invasion was found, and CRP level was an independent indicator of poor prognosis and early recurrence.[11] In ovarian cancer, preoperative CRP was an independent prognostic marker associated with stage and postoperative residual tumor mass.[18] In renal cell carcinoma (RCC), serum CRP was significantly associated with RCC-specific mortality.[15] In esophageal cancer, preoperative high CRP level was associated with tumor progression and poor survival.[8-10] Finally, in colorectal cancer, preoperative elevation of CRP level was an indicator of malignant potential of tumors such as liver metastasis, peritoneal carcinomatosis, lymph node metastasis, and vascular invasion, as well as a predictor of poor prognosis.[12,14] Until now, however, a few data showed the relationship between CRP and treatment outcomes in small cell lung cancer.

In our study, a positive correlation between CRP and weight loss was observed. This is consistent with previous studies, which showed that systemic inflammatory response is associated with increase in resting energy expenditure and loss of lean tissue in patients with lung cancer: Staal-van den

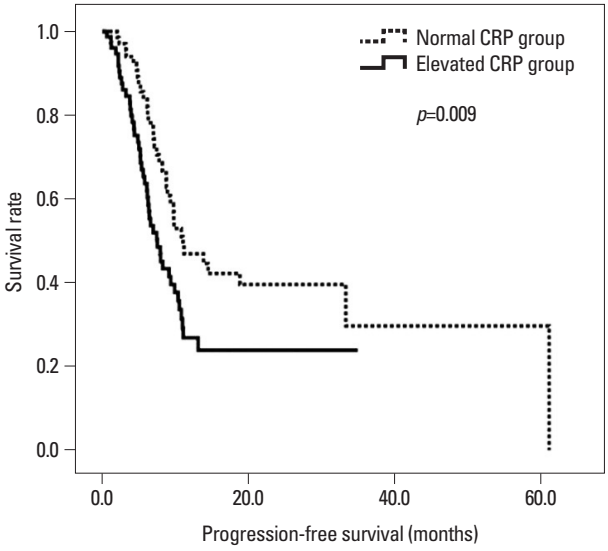

Fig. 2. Kaplan-Meier survival curve for progression-free survival in patients with normal CRP and elevated CRP group. CRP, C-reactive protein.

Brekel, et al.[37] reported that hypermetabolism and weight loss are related to enhanced inflammatory response in SCLC patients. In addition, several studies showed that acute phase response is involved in the pathogenesis of cancer cachexia.[38,39] We also found that extensive disease was associated with high serum CRP level, possibly demonstrating that large tumor burden is likely to increase inflammatory cytokines, such as IL-1, IL-2, tumor necrosis factor-alpha, and interferon-gamma,[2,3] which stimulates CRP production.[18]

In terms of response, the relationship between serum CRP and response was not clear. It is highly possible that pre-treatment serum CRP was not sufficient for predicting chemo-response. Therefore, it is more reasonable to monitor serial serum CRP level, including not only pre-treatment but also during and after the treatment. Milroy, et al.[40] demonstrated that acute phase response during chemotherapy might have a potential for predicting chemo-response in SCLC since chemo-sensitive tumors might result in tumor necrosis, thereby inducing an acute phase reaction, and significant reduction in the level of CRP was observed after chemotherapy.[41]

As for prognosis, elevated serum CRP was associated with reduced OS and PFS, apart from all clinically established prognosticators. This result suggests that it might be a useful marker to define a subset of patients with bad prognosis who require intensive treatment. For example, patients with higher pretreatment CRP within the same stage require more enhanced systemic chemotherapy than lower CRP group patients. In the present study, we found a trend between serum CRP level and survival within each stage: ED with high serum CRP group showed relatively shorter OS

than ED with low serum CRP group (mean OS for high CRP group vs. low CRP group, 19.1 months vs. 23.2 months; p=0.062).

The mechanism by which an inflammatory response is evoked by SCLC is not yet clear. One possible mechanism is coexisting pulmonary infection (or obstructive pneumonia), which could increase white blood cell counts (WBC), subsequently increasing pro-inflammatory cytokine CRP concentration. In the current study, therefore, we evaluated the correlation between WBC and CRP, however, failed to find any significant correlations (pearson correlation coefficient=0.140; p=0.099). This result might explain why infection is not the main stimulus to the increased CRP. The other possibility is that pro-inflammatory cytokines are produced by tumor necrosis or local tissue damage which is caused by the tumor-host cell interaction, however, we are not certain whether those cytokines are produced directly by tumors.

In conclusion, we suggest that pre-treatment serum CRP could be used as a prognostic marker in SCLC patients, and it might complement the prognostic value of stage and performance status. However, the association between CRP and survival outcome might require further investigation, and our result should await internal or external validation before being used in clinical practice, because of the limitations inherent to retrospective study with a small sample size.

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