C-Reactive Protein as a Monitor of Chemotherapy Response in Advanced Non-Small Cell Lung Cancer (CML Study)

Vichien Srimuninnimit MD*, Sarppasit Ariyapanya MD*,
Akarin Nimmannit MD, PhD**, Suwimon Wonglaksanapimon MD***,
Charuwan Akewanlop MD*, Nopadol Soparattanapaisarn MD*

** Division of Medical Oncology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand*
*** Office for Research and Development, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand*
**** Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Objective: *The aim of the present prospective study was to evaluate the correlation between the change of serum c-reactive protein (CRP) levels and response to chemotherapy in patients with locally advanced or metastatic non-small cell lung cancer.*
Material and Method: *Patients with locally advanced or metastatic non-small cell lung cancer who received the first line chemotherapy were measured serum CRP levels prior to treatment. Chemotherapy regimen was given to patients according to physicians and radiologic imaging was evaluated after two or three cycles of treatment. Serum CRP levels were measured first time at pre-treatment and second time in patients who had pre-treatment serum CRP levels greater than normal range (3 mg/l) at the time of response assessment or clinical progression. The primary end point was the correlation between change of serum CRP levels and radiologic response. The secondary end point was the prevalence of elevated CRP levels in advanced NSCLC patients and correlation between initial CRP levels and progression free survival (PFS).*
Results: *Fifty four patients were enrolled. Prevalence of elevated CRP levels in advanced NSCLC was 76%. Thirty patients had serial serum CRP measured. There was correlation between change in serum CRP levels and response to treatment (r = 0.43, p = 0.018, spearman rank). There was significant correlation between response to treatment and decrease in CRP levels greater than 50% (p = 0.009, Fisher's exact test). In contrast there was no correlation between progression and increase in CRP levels (p = 0.640, Fisher's exact test). All patients with serial CRP levels decreased to normal range (< 3mg/l) had response to chemotherapy. High pre-treatment CRP levels (> 100 mg/l) correlated with poor PFS. Median PFS for patients with pre-treatment CRP levels of 3-30 mg/l, 30-100 mg/l and >100 mg/l was 23.0 weeks, 13.0 weeks and 6.3 weeks, respectively. Patients with serial CRP levels less than 3 mg/l had greater PFS than patients with serial CRP levels higher than 3 mg/l (p = 0.026, log rank test).*
Conclusion: *The present study suggested that high levels of pre-treatment serum CRP and persistent CRP in serum was a poor prognostic factor. The decrease in CRP levels greater than 50% was a simple method to predict the response to treatment in patients with locally advanced or metastatic non-small lung cancer.*

Keywords: *C-reactive protein, Lung cancer*

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Lung cancer is the leading cause of cancer death in the world accounting for approximately 1.4 million deaths in 2008[1] and 5 year-survival across all stages of the disease is approximately 14%[2]. The majority of non-small cell lung cancer (NSCLC) patients present with locally advanced or metastatic disease and treatment is only palliative intent. Several prospective trials and meta-analyses are required to prove convincingly that chemotherapy leads to a small but statistically significant improvement in survival when compared with best supportive care only[3]. But only 20-30% of patients treated with combination chemotherapy responded to the treatment[4,5]. Furthermore, treatment with chemotherapy is associated with a number of serious and unpleasant side effects, including nausea and vomiting, myelosuppression, neurotoxicity and renal function

Correspondence to:
Srimuninnimit V, Medical Oncology Division, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: 0-2419-7771

impairment. The guideline for treatment monitoring is based on imaging evaluation after the 2nd or the 3rd cycle of chemotherapy using standardized criteria (RECIST)[6,7]. Unfortunately sometimes when a disease is in progress, chest radiography or even computed tomography (CT) cannot detect the difference among tumor, atelectasis, infectious infiltrates or pleural effusion. Additionally there is a limitation in utility assessment in some center. The main challenge is to detect the early disease progression using a simple method and then provide further treatment for patients with locally advanced or metastatic NSCLC.

C-reactive protein (CRP) is a non-specific marker of inflammation. It was first discovered by Tillet and Francis in 1930 and was named CRP because it reacted with the C-polysaccharide found in plasma during the acute phase of a pneumococcal pneumonia[8]. Many studies found that serum CRP levels have been found to be elevated in patients with many malignancies, implying a correlation between inflammation and malignancy[9-12]. Several possible mechanisms such as tissue inflammation, immune response and cancer inflammatory protein have been proposed for the relationship between CRP and cancer[11]. In NSCLC elevated levels of circulating CRP have been found in 75% to 80% of patients with inoperable NSCLC[13,14]. Recently, many studies in NSCLC use serum CRP levels as predictive factor of cancer risk[11,15-20], predictive factor for operative NSCLC[21] as well as prognostic and predictive factor for advanced NSCLC[14,21-27]. Just only one retrospective study reported the relevance of CRP in advanced NSCLC as an early marker in response to chemotherapy[28].

The primary endpoint of this prospective study was to evaluate the correlation between the change of CRP levels and tumor response by radiological imaging in patients with locally advanced or metastatic non-small cell lung cancer treated with chemotherapy.

Material and Method

Patients

Patients with locally advanced or metastatic non-small cell lung cancer treated with the first-line chemotherapy were enrolled. All patients were older than 18 years old, with histologically proven non-small cell lung cancer, no prior treatment for advanced disease, measurable lesion, WHO performance status of 0 to 2, no serious co-morbidity disease and normal renal and hepatic function. Exclusion criteria included patients with clinical suspected infection defined as fever, microbiologically documented infections and the current administration of antibiotics. Each patient received the first-line chemotherapy regimen according to clinical physicians. Radiographic imaging of the chest (either chest radiography or contrast-enhanced CT) prior to and after 2 or 3 cycles were performed to evaluate the response to chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0)[7]. An independent radiological response review was undertaken to ensure that there was no systematic bias in investigator assessments of progressive disease. The authors obtained written informed consent from all patients before study enrollment. The present study was undertaken in accordance with the ethics principles of the Declaration of Helsinki and was consistent with good clinical practices and applicable laws and regulations.

Methods

A blood sample of serum CRP level concentration was obtained from each patient prior to the first chemotherapy cycle. Serum CRP level concentration was performed in the laboratory of Siriraj hospital using the Nephelometry method. The serial serum CRP level concentration was followed-up only in patients who had pre-treatment serum CRP level greater than 3 mg/l at the time of response assessment or the time of clinical progression. The present study classified the change of CRP levels into four groups, normalization, decrease $\geq$ 50%, unchanged (decreased < 50% or increase < 25%) and increase $\geq$ 25% groups. The time of response assessment was after two or three cycles of chemotherapy according to clinical physicians. Routine laboratory measurement of complete blood count, blood urea nitrogen, creatinine and liver function test was performed. Smoking status was classified as non smokers (defined as smoked < 100 cigarettes in their life) or current smoker (defined as current smoking or stop smoking < 15 years) or former heavy smoker (defined as stop smoking > 15 years previously and > 10 pack- years of smoking) or former light smoker (defined as stop smoking > 15 years previously and $\leq$ 10 pack-years of smoking). The primary endpoint of this prospective study was to evaluate the correlation between the change of CRP levels and tumor response by radiological imaging in patients with locally advanced or metastatic non-small cell lung cancer treated with chemotherapy. The secondary end point was the prevalence of elevated CRP levels in advanced NSCLC patients and correlation

between initial CRP levels and progression free survival (PFS).

Statistics

It was estimated that 70 patients with elevated pre-treatment serum CRP levels greater than normal range (3 mg/l) were required to produce a 90% probability of expected sensitivity and a 9% probability of error, using a two-tailed test with an $\alpha = 0.05$ to detect disease progression. The correlation between the change of CRP levels and response to chemotherapy was calculated using Spearman rank correlation test and the correlation between the change of CRP levels and multiple continuous variable was calculated using Pearson correlation test. The proportion between groups were compared using χ^2 test or by Fisher's exact test or by t-test. The mean value between group was compared using the Wilcoxon-Mann-Whitney test. Receiver operating characteristics (ROCs) were used for the change of CRP levels with response to treatment compared with patients with no response to treatment. The power of CRP was evaluated with the areas under the curve with the 95%CI. The sensitivity, specificity were calculated. Progression free survival was calculated by using Kaplan-Meier method. SPSS version 18.0, MEDCALC and STATCALC statistical software were used.

Results

Patient Characteristics

From March 2010 to December 2010, 56 patients were enrolled (male:female ratio; 1.1:1.0; median age; 61.5 years old). No baseline serum CRP concentration was available in 2 cases. Normal serum CRP concentration was measured in 13 cases, no serial serum CRP was available in 11 cases. No serial serum CRP was measured due to loss to follow-up or death in 6 cases, no blood sampling measurement in 4 cases, and between treatment in 1 case and consequently all remaining 30 patients were included in the analysis (Fig. 1). Patient characteristics were listed in Table 1.

Pre-treatment CRP

Pre-treatment CRP concentration was elevated in 41 of 54 patients (76%). The average CRP levels prior to the first cycle of chemotherapy was 33.70 mg/l (range; 3.12-149.0 mg/l). Smoking patients had a significantly higher prevalence of elevated CRP levels (> 3mg/l) at the beginning of chemotherapy compared with non smokers. No significant correlation was found between prevalence of elevated CRP levels and sex, age, underlying disease, ECOG performance status, histology, staging, tumor size or sites of metastasis. In the group of patients with pre-treatment CRP levels > 3 mg/l, the levels of pre-treatment CRP were slightly correlated with the tumor sizes (Pearson correlation coefficient, 0.399; p = 0.013).

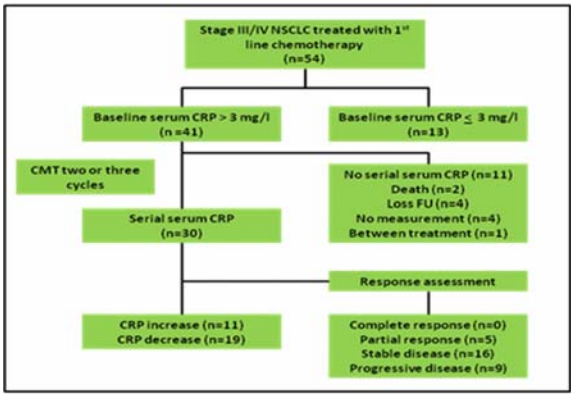

Fig. 1 Diagram for study

Table 1. Patient characteristics

	No.	%
Patients with baseline CRP > 3 mg/l	41	75
Median CRP levels (mg/l)	17.9	
Mean CRP levels (mg/l)	33.7	
Range	3.12-149	
Age (median, years)	62	
Gender		
Male	26	63
Female	15	37
Smoking status		
Non-smoker	16	39
Former heavy smoker	7	17
Current smoker	18	44
ECOG		
PS = 0	10	24
PS = 1	28	68
PS = 2	3	7
Histology		
Adenocarcinoma	28	68
Squamous cell carcinoma	1	2
Large cell carcinoma	1	2
NOS	11	27
TNM staging		
IV	41	100

Radiologic response and the Change of CRP levels

In 30 selected patients, radiographic imaging of the chest and serial serum CRP were performed

during chemotherapy. Chemotherapy was give 1-3 cycles prior to response evaluation (mean, 2.73 cycles). Chemotherapy regimen included platinum plus taxanes (27%), platinum plus gemcitabine (70%) and platinum plus etoposide (3%). Tumor response data were listed in Table 2. The response rate including complete response, partial response, stable disease and progressive disease were 0 case (0%), 5 cases (17%), 16 cases (53%) and 9 cases (30%), respectively. In patients with partial response (PR) the median change of CRP levels was -100% (from 6.57 to 0, p = 0.043), whereas in the cases with stable disease or progressive disease the median change were -44% (from 9.12 to 5.11, p = 0.501) and + 31% (from 20.40 to 26.70, p = 0.953) respectively (Table 3) (Fig. 2).

There was the correlation between the change of CRP levels that categorized into three groups; decrease > 50%, unchanged (decreased < 50% or increase < 25%) and increase > 25% groups and response to treatment defined by RECIST criteria (Spearman rank correlation coefficient, 0.43; p = 0.018).

A significant correlation between response to treatment and decrease in CRP levels greater than 50% can be found (p = 0.009, Fisher's exact test). But there was no correlation between progression and increase in CRP levels greater than 25% (p = 0.640, Fisher's exact test).

For patients with decrease in CRP levels, The authors chose a serial CRP levels turned to < 3 mg/l (decrease-100%) to detect response to treatment, corresponding to a sensitivity of 100% (95% CI 48.0-100.0%), a specificity of 84% (95% CI 63.9-95.4%). The

Table 2. Response evaluation and Change of CRP levels (%)

	Change of CRP levels (%)		
Response	Decrease ≥ 50%	Unchanged	Increase ≥ 25%
Complete response	0	0	0
Partial response	5	0	0
	(100%)	-	-
Stable disease	6	6	4
	(38%)	(38%)	(24%)
Progressive disease	2	4	3
	(22%)	(44%)	(33%)
Response rate	5	0	0
(CR + PR)	(100%)	-	-
Disease control rate	11	6	4
(CR +PR + SD)	(52%)	(29%)	(19%)

Table 3. Response evaluation and serial CRP level

	Pre-treatment CRP (mg/l)		Serial CRP (mg/l)		
Response	Mean (SD)	Median IQR	Mean (SD)	Median IQR	p-value
CR (n = 0)	-	-	-	-	
PR (n = 5)	13.39 (17.62)	6.57 (3.65-26.54)	< 3	< 3	0.043
SD (n = 16)	15.45 (14.48)	9.12 (5.95-21.68)	13.93 (25.52)	5.11 (3.39-12.08)	0.501
PD (n = 9)	53.77 (58.53)	20.4 (12.89-119.45)	74.27 (97.32)	26.7 (10.77-133.00)	0.953

IQR; Interquartile range

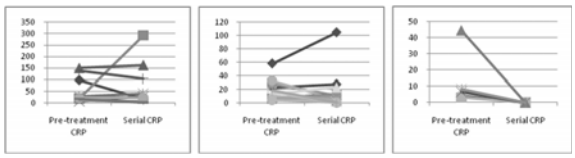

Fig. 2 Linear plot graph A) Progressive disease group, B) Stable disease group, C) Partial response group

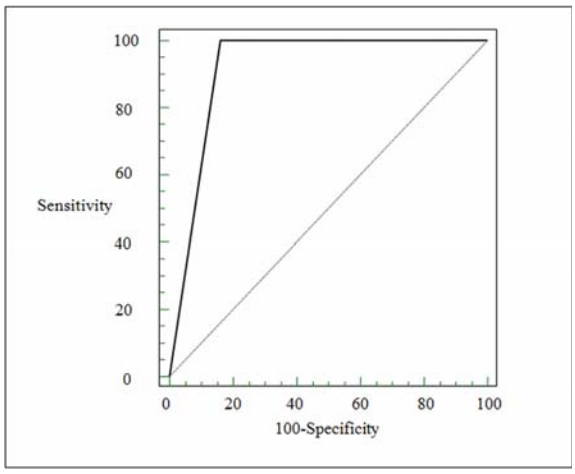

Fig. 3 ROC curve for patients with response to treatment drawn with the decrease in serial CRP

AUC was 0.920 (95% CI 0.761-0.986) (Fig. 3).

CRP and PFS

Pre-treatment CRP levels and documents of disease progression was available in 39 patients. In December 2010, 17 of 39 patients (44%) was progress. The authors found the correlation between pre-treatment CRP levels and progression free survival ($p = 0.004$, log rank test). Median PFS for patients with pre-treatment CRP levels of 3-30 mg/l, 30-100 mg/l and > 100 mg/l was 23.0 weeks, 13.0 weeks and 6.3 weeks, respectively (Fig. 4).

In patients with pre-treatment CRP levels greater than 3 mg/l and serial CRP levels returned to < 3 mg/l had greater progression free survival than patients with still elevated CRP levels ($p = 0.026$, log rank test) (Fig. 5).

Discussion

Serum CRP was found to be elevated in patients with many malignancies. In the present study of locally advanced or metastatic NSCLC patients, the elevated serum CRP concentration prior to systemic treatment was 76% (41/54 patients). This was consistent

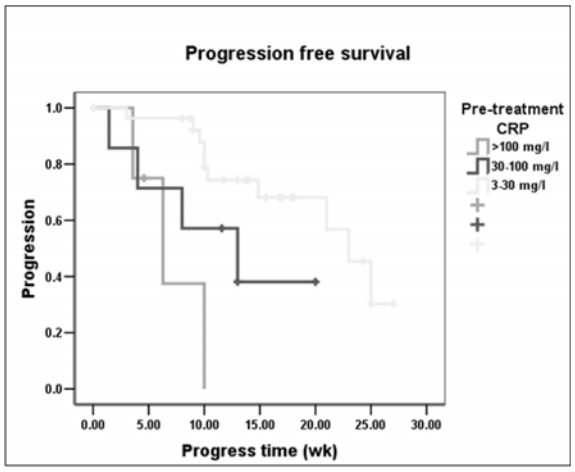

Fig. 4 PFS in patients according to pretreatment CRP (3-30 mg/l, 30-100 mg/l, and >100 mg/l) ($p = 0.004$, log rank test)

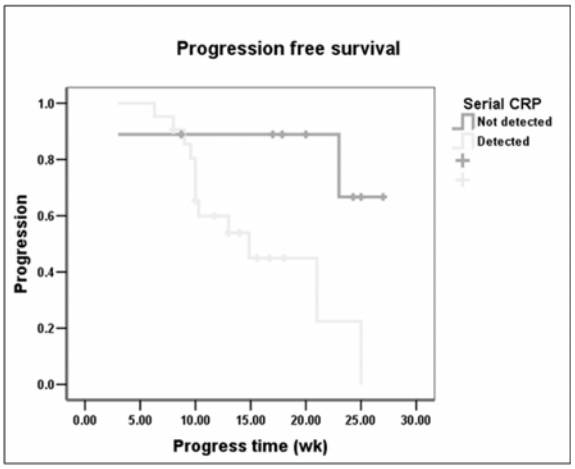

Fig. 5 PFS in patients according to serial CRP (detected group and undetected group) ($p = 0.026$, log rank test)

with previous studies, which showed that 70%-80% of inoperable NSCLC patients had a raised serum CRP[13,14] even though the cut point of value defined raised serum CRP was different. The reasons for CRP elevation in cancer patients were not completely understood but several possible mechanisms had been proposed for the relationship between CRP and cancer[11]. First, tumor growth could cause tissue inflammation and hence increase CRP levels. Second, CRP levels could be used as an indicator of an immune response to tumor antigens. Third, there was evidence that cancer cells could increase the production of inflammatory proteins, which could explain the high CRP concentration in

patients with cancer. In 2008, Jin Gu Lee showed that CRP level was correlate to tumor size in operable NSCLC patients implying that CRP had represented tumor burden[29]. The present study showed the same result.

Although serum CRP concentration was likely to be used as a clinical application, the association between CRP concentration and cancer was likely to be confounded by socioeconomic and lifestyle factors, particularly smoking and body mass index. Serum CRP concentration appeared in the serum of patients with infections or inflammation, during the acute and chronic stages[30,31].

In the present study, there was the significant correlation between elevated serum CRP levels (> 3 mg/l) and history of smoking and the correlation between serum CRP levels and tumor size. Whereas there was no correlation between elevated serum CRP levels and sex, age, underlying disease, ECOG performance status, histology, or sites of metastasis.

The results of many prospective or retrospective studies showed that elevated serum CRP was associated with predictive factor of cancer risk[11,15-20], predictive factor for operative NSCLC[21] as well as prognostic and predictive factor for advanced NSCLC. Elevated CRP has been associated with progressive disease and poor survival for patients with malignancies[9]. In the present study, progression free survival was poor in patients with pre-treatment serum CRP levels greater than 100 mg/l or in patient with still elevated serial serum CRP levels.

The present study demonstrated that the increase in serial CRP levels was not correlated with disease progression but the decrease in serial CRP level greater than 50% was correlated with response to treatment with chemotherapy. Nobody with serial CRP levels decreased to < 3mg/l had disease progression, this result suggested that patients with serial CRP levels decreased to the normal range had potentially response to treatment.

As compared to others serum markers, there was a study demonstrated that carcinoembryonic antigen (CEA) was a useful marker for evaluation of tumor response to chemotherapy with sensitivity of 82% and specificity of 69% but not correlated with disease progression[32]. The result was consistent with the present study. However the present study showed that CRP was higher sensitivity, higher specificity and cheaper than CEA.

To our knowledge, the present study was the first prospective study to evaluate the use of changing CRP levels in the monitoring of patients with NSCLC treated with palliative chemotherapy. Our results suggested that the post-treatment of CRP might be useful in monitoring chemotherapy response in patients with locally advanced or metastatic NSCLC especially in the doubtful imaging evaluation.

The present study had some limitations. The number of cases were too small to provide a precise estimate of the association between response and the decrease of serial CRP levels.

Currently, the standard evaluation method by CT scan remains limit in some situations to define response to treatment, new methods are being developed, such as metabolic imaging (positron emission tomography). In comparison with these new technologies, the main advantage of CRP is its low cost, ease to use and accessibility.

In conclusion the serial CRP monitor holds promise to optimize treatment evaluation of patients with locally advanced or metastatic NSCLC. A future multicenter study with a large patient population is warranted to confirm our results.

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Potential conflicts of interest

None.

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การติดตามการรักษาด้วยค่าซีอาร์พีในผู้ป่วยมะเร็งปอดชนิดที่ไม่ใช่เซลล์ขนาดเล็กในระยะลุกลามที่ได้รับการรักษาด้วยเคมีบำบัด

วิเชียร ศรีมุนินทร์นิมิต, สรรพสิทธิ์ อริยปัญญา, สุวิมล วงศ์ลักษณะพิมล, อัครินทร์ นิมมานนิตย์, จารุวรรณ เอกวัลลภ, นพดล โสภารัตนาไพศาล

วัตถุประสงค์: *เพื่อศึกษาความสัมพันธ์ระหว่างค่าซีอาร์พีในเลือดกับการตอบสนองต่อการรักษาด้วยยาเคมีบำบัดในผู้ป่วยมะเร็งปอดระยะลุกลาม*

วัสดุและวิธีการ: *ผู้ป่วยมะเร็งปอดชนิดที่ไม่ใช่เซลล์ขนาดเล็กที่ได้รับการรักษาด้วยยาเคมีบำบัด ณ โรงพยาบาลศิริราช จะได้รับการเจาะเลือดค่าซีอาร์พีร่วมกับการประเมินภาพทางรังสีเป็นพื้นฐาน ผู้ป่วยทุกรายจะได้รับการรักษาตามมาตรฐานการรักษา เฉพาะผู้ป่วยที่มีค่าซีอาร์พีในเลือดระดับพื้นฐานสูงกว่าปรกติ (> 3 มิลลิกรัมต่อลิตร) จะได้รับการประเมินค่าซีอาร์พีในเลือดเป็นครั้งที่สองพร้อมกับการประเมินภาพทางรังสีเพื่อดูการตอบสนองต่อการรักษา*

วัตถุประสงค์หลักเพื่อดูความสัมพันธ์ระหว่างการเปลี่ยนแปลงค่าซีอาร์พีในเลือดกับการตอบสนองต่อการรักษาโดยภาพทางรังสี วัตถุประสงค์รองเพื่อดูความชุกของการเพิ่มขึ้นของค่าซีอาร์พีในผู้ป่วยมะเร็งปอดชนิดที่ไม่ใช่เซลล์ขนาดเล็กในระยะลุกลาม และเพื่อดูความสัมพันธ์ระหว่างค่าซีอาร์พีกับการดำเนินโรค

ผลการศึกษา: *ผู้ป่วยจำนวน 54 คน เข้าร่วมการศึกษาพบว่ามีความชุกของการเพิ่มขึ้นของค่าซีอาร์พีในเลือด 76 เปอร์เซ็นต์ ผู้ป่วยจำนวน 30 คน ได้รับการเจาะค่าซีอาร์พี 2 ครั้ง และเปรียบเทียบกับการตอบสนองต่อการรักษาด้วยภาพทางรังสีพบว่ามีความสัมพันธ์โดยที่ค่า relative คือ 0.43 (p = 0.018, Spearman rank) และพบมีความสัมพันธ์ระหว่างการลดลงของค่าซีอาร์พีในเลือดมากกว่า 50 เปอร์เซ็นต์กับการตอบสนองต่อการรักษา (p = 0.009, Fisher's exact test) แต่ไม่พบความสัมพันธ์ระหว่างการเพิ่มขึ้นของค่าซีอาร์พีในเลือดกับการลุกลามของโรคมะเร็งปอด (p = 0.640, Fisher's exact test) ผู้ป่วยที่มีค่าซีอาร์พีต่ำกว่า 3 มิลลิกรัมต่อลิตร ในการเจาะเลือดครั้งที่สองพบว่าทุกคนตอบสนองต่อการรักษา*

ในแง่การดำเนินโรคพบว่าผู้ป่วยที่มีค่าซีอาร์พีก่อนการรักษาในระดับสูงมีการดำเนินโรคที่ไม่ดีกว่า โดยพบว่าผู้ป่วยที่มีค่าซีอาร์พีก่อนการรักษาที่ระดับ 3-30 มิลลิกรัมต่อลิตร, 30-100 มิลลิกรัมต่อลิตร, และ > 100 มิลลิกรัมต่อลิตร มีค่ามัธยฐานของระยะเวลาในการลุกลามของตัวโรค (median progression free survival) เท่ากับ 23.0 สัปดาห์, 13.0 สัปดาห์ และ 6.3 สัปดาห์ตามลำดับ ผู้ป่วยที่มีค่าซีอาร์พีในเลือดหลังการรักษาต่ำกว่า 3 มิลลิกรัมต่อลิตร จะมีค่ามัธยฐานของระยะเวลาในการลุกลามของตัวโรค ดีว่าผู้ป่วยที่ยังตรวจพบค่าซีอาร์พีในเลือดมากกว่า 3 มิลลิกรัมต่อลิตรหลังการรักษา (p = 0.026, log rank test)

สรุป: *ค่าซีอาร์พีในเลือดที่สูงก่อนการรักษาและค่าซีอาร์พีที่มากกว่า 3 มิลลิกรัมต่อลิตรหลังการรักษาเป็นตัวพยากรณ์โรคที่ไม่ดีในผู้ป่วยมะเร็งปอดที่ไม่ใช่เซลล์ขนาดเล็ก การลดลงของค่าซีอาร์พีในเลือดมากกว่า 50 เปอร์เซ็นต์ของผู้ป่วยมะเร็งปอดระยะลุกลามที่ได้รับการรักษาด้วยยาเคมีบำบัด เป็นวิธีที่ง่ายและสะดวกในการบอกว่าผู้ป่วยน่าจะตอบสนองต่อการรักษา*