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NORIKO TAKEDA, KAZUHISA ASAI, NAOKI IJIRI, NORIO YAMAMOTO, TETSUYA WATANABE, HIROSHI KAMOI, HIROSHI KANAZAWA, and KAZUTO HIRATA

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Noriko Takeda, Kazuhisa Asai, Naoki Ijiri, Norio Yamamoto,
Tetsuya Watanabe, Hiroshi Kamoi, Hiroshi Kanazawa, and Kazuto Hirata

Department of Respiratory Medicine, Osaka City University, Graduate School of Medicine

Abstract

Background

Pentraxin-3 (PTX3) is a newly discovered biomarker for various inflammatory conditions. We measured plasma PTX3 levels in patients with febrile neutropenic lung cancer and examined the utility of PTX3 levels as a biomarker for febrile neutropenia.

Methods

Fourteen patients with febrile neutropenic lung cancer were enrolled in the study. In addition, 10 untreated lung cancer patients and 12 healthy adults were enrolled as a disease control group and a healthy control group, respectively. On the day of onset of febrile neutropenia (day 1) and days 3 and 7, PTX3 and C-reactive protein (CRP) levels were measured. In the control groups, PTX3 and CRP levels were measured once.

Results

On day 1, plasma CRP levels in febrile neutropenia during chemotherapy or chemoradiotherapy for lung cancer (FN/LC) patients (8.11±6.42 mg/dL) were significantly higher than those in healthy controls (HC) and chemotherapy/chemoradiotherapy-naïve lung cancer (CN/LC) patients ($p<0.05$). However, CRP levels of the CN/LC group (0.33±0.02 mg/dL) were also significantly higher than those of the HC group (0.07±0.09 mg/dL) ($p<0.05$). In contrast, plasma PTX3 levels of the FN/LC group (6.14±5.28 ng/mL) were significantly higher than those of the HC and CN/LC groups on day 1 ($p<0.05$), but PTX3 levels of the CN/LC group (1.60±0.64 ng/mL) were not significantly higher than those of the HC group (1.05±0.25 ng/mL). In the FN/LC group, PTX3 levels peaked immediately on day 1.

Conclusions

PTX3 may be a useful biomarker for diagnosis of FN in patients with LC.

Key Words: Lung cancer; Febrile neutropenia; C-reactive protein (CRP); Pentraxin-3 (PTX3)

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Correspondence to: Kazuhisa Asai MD, PhD.
Department of Respiratory Medicine, Osaka City University, Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3916; Fax: +81-6-6646-6160
E-mail: kazuasai@med.osaka-cu.ac.jp

Introduction

In 2013, there were approximately 72.700 deaths due to lung cancer (LC) in Japan (Vital Statistics Japan (Ministry of Health, Labour and Welfare)). Lung cancer is the leading cause of death among men and the second leading cause of death among women. The National Cancer Center of Japan reported that stages 0, Ⅰ, Ⅱ, Ⅲ, Ⅳ, and "unknown" accounted for 0.1%, 38.9%, 7.9%, 16.6%, 32.6%, and 3.8% of LC cases diagnosed in 2012, respectively (http://ganjoho.jp/data/professional/statistics/hosp_c_registry/2012_report.pdf). When they were first diagnosed, over half of patients presented with advanced-stage LC (stage Ⅲ or Ⅳ). Four treatment modalities are available for LC: surgery, chemotherapy, radiotherapy, and combination therapy. For advanced-stage cases, chemotherapy and chemoradiotherapy are the only effective options for treatment. Chemotherapy is a systemic therapy that can cause systemic side effects. While nausea, vomiting, alopecia, and some other side effects can be managed with symptomatic treatments, other side effects such as liver dysfunction, drug-induced lung injury, bone marrow suppression, and febrile neutropenia (FN) can threaten the life of the patients. FN, which can lead to life-threatening septicemia and death, is especially dangerous in this regard. During chemotherapy, FN occurs in 6%-12.7% of patients with LC[1,2]. To facilitate timely and appropriate treatment, FN must be detected early and its severity must be evaluated with precision. Therefore, a biomarker for FN is needed. FN is diagnosed according to the patient's peripheral neutrophil count and body temperature[3,4]. In clinical practice, we measure leukocyte counts and C-reactive protein (CRP) levels to esrtimate the intensity of inflammation[5]. CRP is an acute-phase protein produced de novo by the liver in response to interleukin-6 (IL-6). IL-6 is mainly produced by leukocytes at local inflammatory sites, and its production sometimes has a delayed peak. Pentraxin-3 (PTX3), a member of the pentraxin family, is produced by somatic cells, such as epithelial and endothelial cells, in addition to inflammatory cells[6,7]. Therefore, PTX3 might be a rapid and direct indicator of local inflammation[2]. In this study, we measured plasma PTX3 levels in patients with febrile neutropenia during chemotherapy or chemoradiotherapy for lung cancer (FN/LC) and examined the utility of PTX3 as a biomarker for FN.

Materials and methods

Subjects and sample collection

Fourteen FN patients undergoing chemotherapy or chemoradiotherapy for LC were enrolled in this study. Chemotherapy and chemoradiotherapy were performed in an inpatient setting for high-risk LC patients, including elderly patients and patients with multiple complications. All patients with FN were treated in the respiratory ward of Osaka City University Hospital and were prospectively enrolled in this study between April 2010 and March 2011. A variety of patient and tumor characteristics were recorded, such as histological diagnosis, clinical stage (Union for International Cancer Control criteria, 7th edition), performance status, medical history, and family history. To provide a LC control group, we enrolled 10 chemotherapy/chemoradiotherapy-naïve lung cancer (CN/LC) patients who presented no signs of infection. To provide a healthy control group, 12 healthy volunteers were also enrolled. This study was approved by the ethics committee of Osaka City University (Approval number 1569) and all subjects provided written informed consent. Febrile neutropenic patients were enrolled consecutively during chemotherapy or chemoradiotherapy. Blood samples (serum and plasma) for PTX3 measurement were collected using heparin-ethylenediaminetetraacetic acid (commonly known as EDTA) tubes on the day of diagnosis (day 1). FN was diagnosed according to

the domestic criteria of the Japanese Society of Medical Oncology, which are nearly identical to the criteria of the Infectious Diseases Society of America (IDSA). Specifically, FN was defined as an absolute neutrophil count of <500/μL or <1000/μL with a trend toward <500/μL. Fever was defined as a single oral temperature of ≧38℃ or a single armpit temperature of ≧37.5℃[8,9]. Two sets of blood cultures, a sputum culture, and a urine culture were performed to detect bacteremia or infection sites. A chest radiograph was taken to detect pneumonia. After initial laboratory evaluation, administration of granulocyte-colony stimulating factor (G-CSF) and empirical antibiotics (cefepime or meropenem) was started, as recommended by both the IDSA and the domestic guidelines for treatment of FN[8,9]. On days 3 and 7, follow-up evaluations were performed, including laboratory examinations and observations of the patients' conditions. Blood samples for PTX3 measurement were also collected on days 3 and 7. Serum and plasma samples were stored at −80℃ for further analysis. Administration of G-CSF and empirical antibiotics was generally continued until patients had recovered from FN (absolute neutrophil count >5000/μL without fever). However, the exact duration of treatment was decided by the attending physician (NT,KA,NI,TW).

Sample size and power determination

The minimum sample size was initially estimated with GraphPad StatMate 2.0 (Power test) software, which indicated n=12 patients with a power of 95% and a significance level (alpha) of 0.05. To account for withdrawals of consent (predicted rate: 10%) and losses due to sampling on days 3 and 7, we selected a sample size of 14 patients.

Enzyme-linked immunosorbent assay for plasma PTX3 and serum CRP levels

Plasma PTX3 levels were measured by sandwich-type enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (DPTX30; R&D Systems, Minneapolis, MN, USA), according to the manufacturer's instructions. The minimum detectable concentration of PTX3 is 0.78 ng/mL. All samples were analyzed in duplicate. In healthy Japanese populations, PTX3 levels are reported to be approximately 1.87 ng/mL for men and 2.12 ng/mL for women[8].

Serum CRP levels were also measured by ELISA using a commercially available kit (DCRP00; R&D Systems, Minneapolis, MN, USA), according to the manufacturer's instructions.

Definitions of clinical febrile neutropenia parameters (FN parameters)

FN period was defined as the number of days between diagnosis of FN (according to domestic criteria) and recovery. Febrile period was defined as the number of days a single oral temperature of ≧38℃ or a single armpit temperature of ≧37.5℃ was observed. Drug therapy period was defined as the number of days G-CSF and antibiotics were administered.

Statistical analysis

To compare groups, we conducted a parametric one-way analysis of variance (one-way ANOVA) and a nonparametric Kruskal-Wallis test. A post-hoc Bonferroni adjustment was applied to the results of both the ANOVA and the Kruskal-Wallis test. Statistical significance was set at $p<0.05$. Pearson's correlation coefficient and Spearman's rank correlation coefficient were used to determine associations between 2 parameters. Statistical analyses were performed using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The characteristics of the study population are presented in Table 1. The total population consisted

Table 1. Characteristics of each group

	HC	CN/LC	FN/LC	p-value
Subject number	12	10	14	NA
Gender (male/female)	5/7	7/3	12/2	<0.05
Age (years)	53.5±2.0	67.2±2.0	69.9±7.4	<0.05
BMI (kg/m^2)	NA	20.6±2.0	21.7±2.8	NS
PS (0/1/2/3/4)	NA	0/6/0/0/0	4/7/3/0/0	NS
Smoking status (pack/year)	NA	33.3±11.9	63.8±45.5	NS
COPD (−/+)	NA	8/2	4/10	<0.05
Lung cancer stage (ⅡB/ⅢA/ⅢB/Ⅳ)	NA	0/2/2/6	2/6/0/6	NS
Pathology (AD/SQ/SCLC)	NA	2/5/3	3/7/4	NA
Radiation (−/+)	NA	NA	10/4	NA
Regimen number (0/1/2/3)	NA	NA	0/10/1/3	NA

HC, helthy controls; CN/LC, chemotherapy/chemoradiotherapy-naïve lung cancer; FN/LC, febrile neutropenia during chemotherapy or chemoradiotherapy for lung cancer; BMI, body mass index; PS, performance status; COPD, chronic obstructive pulmonary disease; AD, adenocarcinoma; SQ, squamous cell carcinoma; and SCLC, small cell carcinoma. Values are presented as mean±SD.

Table 2. The characteristics of patients with febrile neutropenia by lung cancer treatment

Patients #	Age	Gender	Pathology	Treatment
1	80	male	SQ	DTX
2	74	male	SQ	CDDP/VNR
3	53	female	SQ	GEM
4	73	male	SQ	CBDCA/PTX
5	75	male	SCLC	CBDCA/Vp16
6	73	male	SCLC	AMR
7	73	male	SQ	CBDCA/PTX/RT
8	58	male	AD	CBDCA/PTX/RT
9	71	female	SCLC	CDDP/VP16
10	74	male	SQ	CBDCA/PTX
11	65	male	AD	CBDCA/PTX/RT
12	76	male	AD	CDDP/VNR
13	67	male	SQ	AMR
14	66	male	SCLC	CDDP/VP-16/RT

SQ, squamous cell carcinoma; SCLC, small cell carcinoma; AD, adenocarcinoma; DTX, docetaxel; CDDP, cisplatin; VNR, vinorelbine; CBDCA, carboplatin; GEM, gemcitabine; PTX, paclitaxel; AMR, amrubicin; VP-16, etoposido; and RT, radiation treatment.

of 36 subjects: 14 patients with FN/LC, 10 CN/LC patients, and 12 healthy volunteers (HC). The mean age of the HC group was lower than that of the CN/LC or FN/LC group ($p<0.05$). The proportion of women was similar between the HC and CN/LC groups, but the FN/LC group had significantly fewer women than the HC group ($p<0.05$). Although body mass index, performance status, smoking history, and clinical stage were similar between the 2 LC groups, the prevalence of chronic obstructive pulmonary disease (COPD) was significantly higher in the FN/LC group ($p<0.05$).

Table 2 presents the detailed characteristics of the FN/LC group, which was composed of 12 men and 2 women. Pathological diagnoses in this group included squamous cell carcinoma (n=7), adenocarcinoma (n=3), and small cell carcinoma (n=4). Of the 14 patients, 4 had received

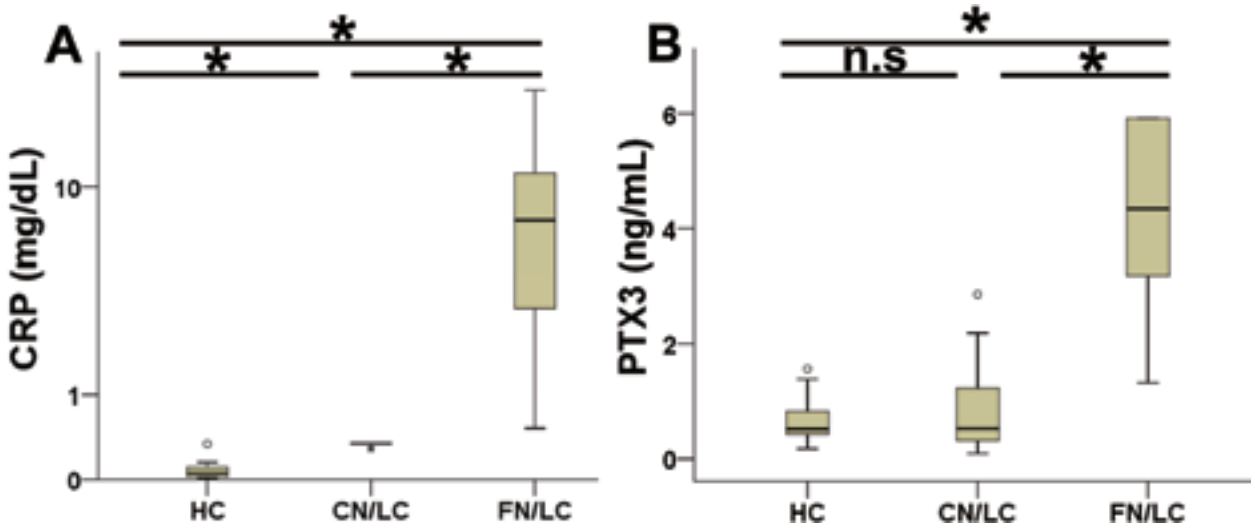

Figure 1. Plasma C-reactive protein (CRP) and Pentraxin-3 (PTX3) levels on febrile neutropenia (FN) on day 1. Plasma CRP levels in the chemotherapy/chemoradiotherapy-naïve lung cancer (CN/LC) group were significantly higher than those in the healthy control (HC) group on day 1 (A). Plasma CRP levels in febrile neutropenia during chemotherapy or chemoradiotherapy for lung cancer (FN/LC) group was significantly higher than those in CN/LC group (A). The plasma PTX3 levels in the FN/LC were significantly higher than the HC and CN/LC group on day 1 ($p<0.05$). There were no significant difference between plasma PTX3 levels in the CN/LC group and those in the HC group (B).

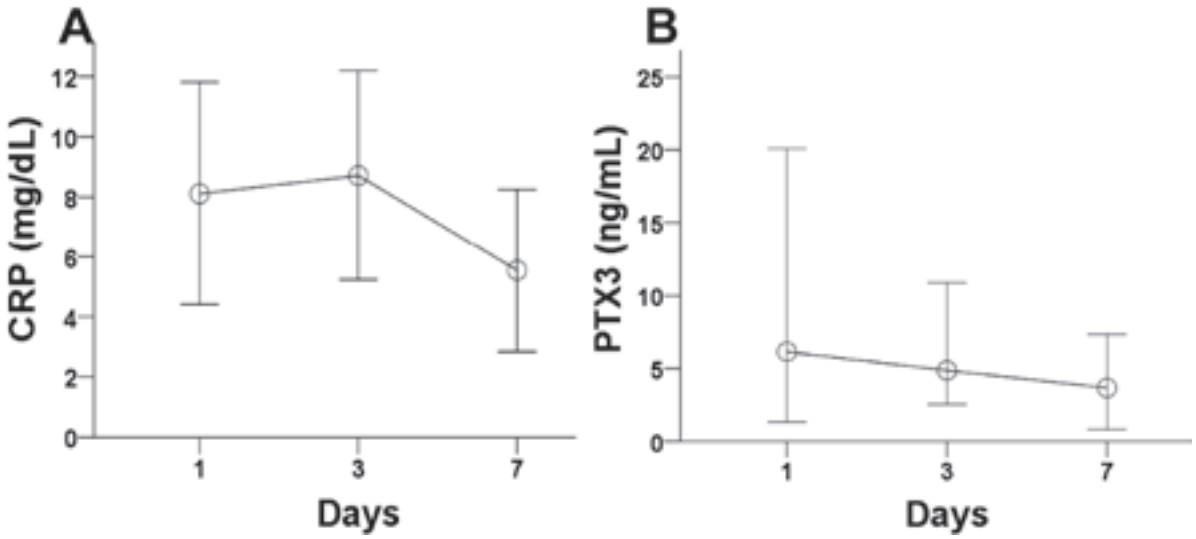

Figure 2. The changes of C-reactive protein (CRP) and Pentraxin-3 (PTX3) levels by days. This figure shows the change of CRP (A) and PTX3 (B) levels with days from diagnosis of febrile neutropenia (FN). The peaks of CRP and PTX3 levels were different. Two parameters might depend on different regulatory mechanism.

chemoradiotherapy.

CRP and PTX3 levels in study subjects

CRP and PTX3 levels are presented in Figure 1. On day 1, CRP levels in the FN/LC group (8.11±6.42 mg/dL) were significantly higher than those in the HC and CN/LC groups ($p<0.05$). However, CRP levels in the CN/LC group (0.33±0.02 mg/dL) were also significantly higher than those in the HC group (0.07±0.09 mg/dL) ($p<0.05$) (A). In contrast, PTX3 levels in the FN/LC group (6.14±5.28 ng/mL) were significantly higher than those in the HC and CN/LC groups on day 1 ($p<0.05$), but

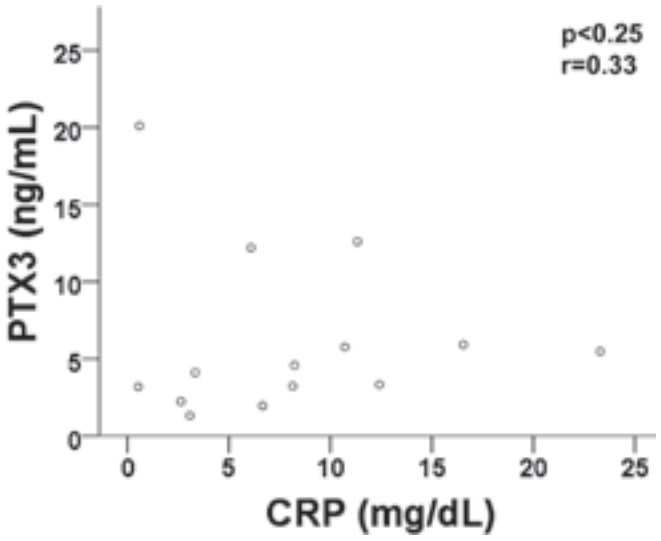

Figure 3. The correlation between C-reactive protein (CRP) levels and Pentraxin-3 (PTX3) levels on day 1 in febrile neutropenia during chemotherapy or chemoradiotherapy for lung cancer (FN/LC) group. There was no correlation between CRP levels and PTX3 levels on day 1 in FN/LC group.

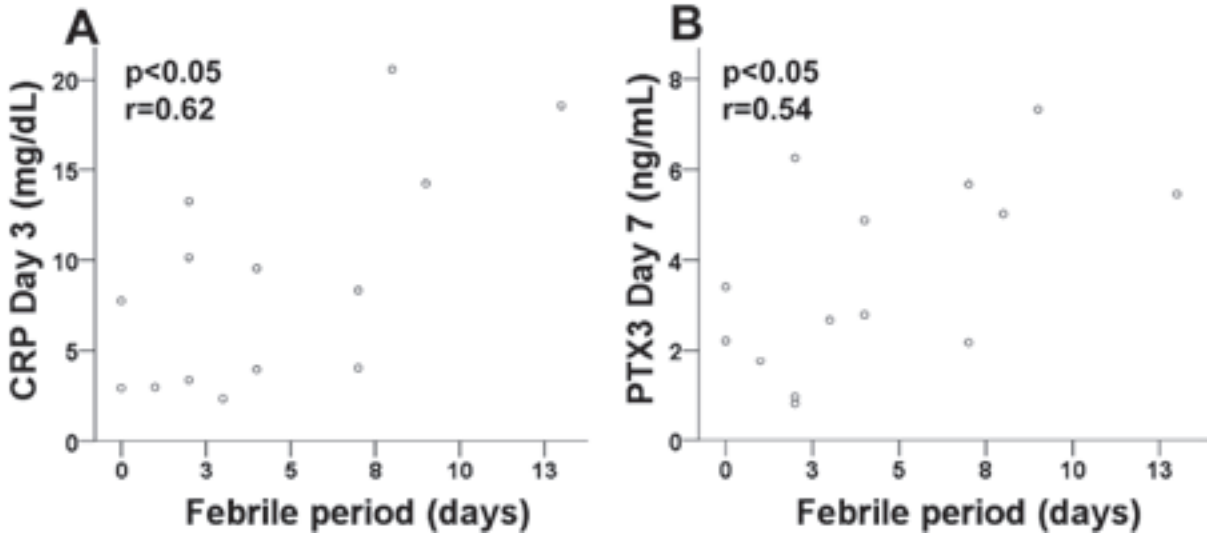

Figure 4. The correlation between febrile period and C-reactive protein (CRP) levels on day3 and Pentraxin-3 (PTX3) levels on day7 in febrile neutropenia during chemotherapy or chemoradiotherapy for lung cancer (FN/LC) group. There were significant correlations between febrile period as one FN parameter and CRP levels on day 3 and PTX3 levels on day 7. However, there were no significant correlations between another FN parameters and CRP/PTX3 levels on other days.

PTX3 levels in the CN/LC group (1.60±0.64 ng/mL) were not significantly higher than those in the HC group (1.05±0.25 ng/mL) (B).

Figure 2 presents changes in CRP levels and PTX3 levels on day 1 and after FN was diagnosed. Comparing days 1, 3, and 7, CRP levels in the FN/LC group were the highest on day 3 (A). In contrast, PTX3 levels in the FN/LC group peaked as early as day 1 and subsequently decreased over the course of the FN period (B). However, the changes in PTX3 levels were not statistically significant.

Figure 3 presents the correlations between same-day CRP and PTX3 levels in the FN/LC group.

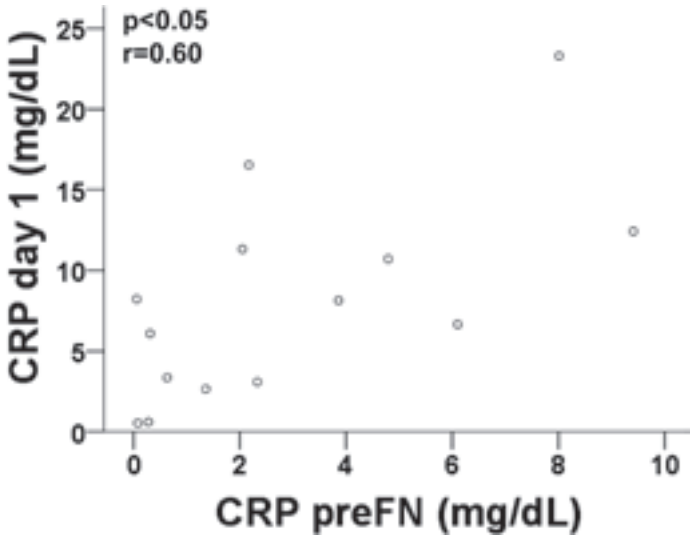

Figure 5. The correlation between pre febrile neutropenia (FN) C-reactive protein (CRP) levels and CRP levels on day 1 in febrile neutropenia during chemotherapy or chemoradiotherapy for lung cancer (FN/LC) group. There was significant correlation between pre FN CRP levels and CRP levels on day 1

No significant correlation between CRP and PTX3 levels was observed on day 1 ($p=0.25$: $r=0.33$). However, there were significant correlations between CRP and PTX3 levels on day 3 ($p<0.05$: $r=0.60$) and day 7 ($p<0.05$: $r=0.67$). Although there were no significant correlations between CRP levels on days 1, 3, and 7, a significant correlation was evident between pre-FN CRP levels and CRP levels on day 1. No significant correlations were observed between PTX3 levels on different days.

Figure 4 presents the significant correlation between febrile period as one FN parameter and CRP levels on day 3 (A) and PTX3 levels on day 7 (B). There were no significant correlations nother FN parameters (FN period and drug therapy period) and CRP/PTX3 levels on other days.

Figure 5 presents the significant correlation between pre FN CRP levels and CRP levels on Day 1.

Discussion

In this study, we measured levels of a newly discovered inflammatory biomarker, PTX3, in patients with FN who were undergoing chemotherapy or chemoradiotherapy for LC. We evaluated the potential of PTX3 as a diagnostic and predictive biomarker for FN, in comparison with CRP. FN is defined as febrile status during a period of neutropenia. The diagnosis of FN is not difficult. In general, the leukocyte count, CRP level, or erythrocyte sedimentation rate is used as a marker of inflammation[5]. However, there is no established biomarker for the early diagnosis and predictive evaluation of FN.

CRP production depends on an inflammatory mediator produced by leukocytes. Therefore, CRP levels can be affected by neutropenia and may be an inaccurate marker of inflammation in patients with this condition. In the FN/LC group in this study, CRP levels at the onset of FN were significantly higher than CRP levels before FN. However, CRP levels increased further on day 3. In contrast, comparing PTX3 levels on days 1, 3, and 7, we found that PTX3 peaked at the onset of FN and subsequently decreased during the FN period.

Unfortunately, patients in the FN/LC group were enrolled in this study at the onset of FN. Consequently, pre-FN PTX3 levels were not available for patients in the FN/LC group. However,

PTX3 levels in the FN/LC group were significantly higher than those in the CN/LC group, and additionally, PTX3 levels increased significantly at the onset of FN and correlated closely with FN duration. The difference between the levels of CRP and PTX3 could be attributable to the different mechanisms by which they are produced (for example, from leukocytes versus source cells). We conclude that PTX3 was rapidly produced in response to FN.

Furthermore, although we found no significant difference in PTX3 levels between the HC and CN/LC groups, CRP levels in the CN/LC group were significantly higher than those in the HC group. It follows that CRP levels in LC patients may be increased by LC itself[11]; indeed, patients in the CN/LC group showed no signs of infection. CRP acts as a multimodal inflammatory alert, and a wide variety of situations can induce CRP production by hepatocytes. Therefore, CRP levels are not highly specific to infection or FN.

We also observed significant correlations between pre-FN CRP levels and CRP levels on day 1. We found that patients' CRP levels at the onset of FN were strongly affected by their previous condition (i.e., before development of FN). Therefore, CRP levels are not suitable for evaluating the severity or diagnostic of FN. Reporting a significant correlation between CRP levels and LC progression, Ming suggested that CRP could be used as a total prognostic marker for LC[9]. Yet, as a prognostic marker for FN, PTX3 is a better choice than CRP.

The gene encoding PTX3, a member of the pentraxin family, was first described as tumor necrosis factor-stimulated gene-14 (TSG-14) by Jonas Emsley in 1994[12]. The pentraxins are acute-phase proteins with a common C-terminal domain. The pentraxin family is composed of 2 subfamilies: short pentraxins such as CRP and serum-amyloid P, and long pentraxins such as PTX3[13]. The short pentraxins are produced by hepatocytes in response to increased systemic inflammatory signals, mainly IL-6 (which is itself produced by inflammatory cells). CRP is now widely used as an inflammatory marker in clinical practice. In contrast to short pentraxins, PTX3 has a longer N-terminal domain, in addition to the common C-terminal domain, resulting in its classification as a long pentraxin. PTX3 is not produced by hepatocytes but by somatic cells, including smooth muscle cells, fibroblasts, dendritic cells, endothelial cells, and epithelial cells[14,15]. It is produced in response to local inflammatory signals, lipopolysaccharide, interleukin-1 (IL-1), and tumor necrosis factor α. CRP binds to the extracellular matrix (i.e., phosphocholine), DNA, chromatin, and complement components such as C1q[16]. After binding, CRP initiates the classical complement pathway, which leads to the elimination of bacteria. PTX3 also binds to certain complement components such as C1q, C4b-binding proteins, and factor H[16,17]. Therefore, PTX3 is not only involved in complement activation but also acts as a complement inhibitor to regulate excessive complement activation[18].

Under physiological conditions, levels of PTX3 circulating in the peripheral blood are as low as approximately 2 ng/mL[14]. Our observations in this study were consistent with these low levels. However, PTX3 levels are known to increase rapidly under inflammatory conditions such as sepsis, endotoxin shock, and some infections. In the case of sepsis, plasma PTX3 increases dramatically, reaching levels as high as 100 ng/mL. Moreover, it has been demonstrated that PTX3 levels correlate with mortality from sepsis[20-23].

There were several limitations to our study. First, our study population was relatively small, especially in the FN/LC group. Correlations of CRP and PTX3 levels with FN parameters were not statistically significant, but this may have been a result of the small sample size in this study. During well-controlled chemotherapy and chemoradiotherapy regimens, FN occurs in 6%-12.7% of

patients with LC[1,2]. The number of FN/LC patients is therefore limited in single-center studies such as our own. Second, there were significant differences in age between the HC group and the LC groups, because LC is usually diagnosed in older patients. Although there was no significant difference in age between the CN/LC and FN/LC groups, patients in the HC group was significantly younger. As far as we know, the relationship between age and PTX3 levels has not been studied. Age differences could introduce some bias into our results. Some limitations were also present in the LC patient groups. The FN/LC group included 6 patients with stage ⅢA LC and 6 patients with stage Ⅳ LC. These patients had already received several serial chemotherapy or chemoradiotherapy treatments. To our knowledge, no studies have been conducted to determine the influence of clinical stage or treatment regimen on PTX3 levels. Third, all patients had recoverd, we could not assess FN mortality. Finally, the prevalence of COPD was significantly higher in the FN/LC group than in the CN/LC group. Although comorbidity with COPD is a risk factor for FN in patients with LC, the effect of COPD on PTX3 levels is unknown.

In this study, we found that levels of the inflammatory biomarker PTX3 increased significantly more rapidly than levels of CRP at the onset of FN. In contrast to CRP levels, PTX3 levels were not significantly affected by LC itself. We conclude that PTX3 is a promising biomarker for FN in patients with LC. Additional studies at a larger scale are warranted.

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