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The Measurements of Plasma Cytokines in Radiation-induced Pneumonitis in Lung Cancer Patients

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Purpose : To investigate whether changes in plasma concentrations of transforming growth factor-β1 (TGF-β1), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) could be used to identify the development of radiation-induced pneumonitis in the lung cancer patients.

Methods and Materials : Seventeen patients with lung cancer (11 NSCLC, 6 SCLC) were enrolled in a prospective study designed to evaluate clinical and molecular biologic correlation of radiation-induced pneumonitis. The study began in May 1998 and completed in July 1999. All patients were treated with radiotherapy with curative intent : 1.8 Gy per day, 5 fractions per week. Serial measurements of plasma TGF-β1, TNF-α and IL-6 were obtained in all patients before, weekly during radiotherapy and at each follow-up visits after completion of treatment. These measurements were quantified using enzyme linked immunosorbent assay (ELISA). All patients were evaluated for signs and symptoms of pneumonitis at each follow-up visit after completion of radiotherapy. High resolution CT (HRCT) scans were obtained when signs and symptoms of pneumonitis were developed after completion of radiotherapy.

Results : Thirteen patients eventually developed signs and symptoms of clinical pneumonitis while four patients did not. TGF-β1 levels were elevated in all 13 patients with pneumonitis, which showed characteristic pattern of elevation (38.45 ng/ml at pretreatment, 13.66 ng/ml during radiotherapy, then 60.63 ng/ml at 2-4 weeks after completion of radiotherapy). The levels of TNF-α and IL-6 were also elevated in the group of patients who developed pneumonitis but the pattern was not characteristic.

Conclusions : Changes in plasma TGFβ-1 levels before, during and after radiotherapy appears to be a useful means by which to identify patients at risk for the development of symptomatic pneumonitis. Other cytokines like TNF-α and IL-6 shows no meaningful changes in association with radiation pneumonitis.

Key Words : Radiotherapy, Radiation Pneumonitis, Cytokines

INTRODUCTION

It is well known that the tolerance of normal tissues to irradiation usually limits the application of tumoricidal doses in radiotherapy. The radiation injury of normal lung tissues is a prime example for this limitation and has been the subject of keen interest in the recent literature. Although much work has been focused on the response of normal lung tissue to radiation dose and volume, the relationship between the onset of radiation pneumonitis and other factors like cytokine cascades has not been clearly understood yet. In several literature, cytokines like TGF-β1 has been reported to be increased in a variety of clinical settings including radiotherapy and may be useful in predicting individualized patient's risk for developing late radiation-induced normal tissue injury.[1~4] Other cytokines like TNF-α and several interleukins (IL-1, IL-6, IL-8) are also regarded as having some roles in association with lung injury to radiation.[5, 6]

Therefore, in the presenting study, we have done a prospective study to evaluate the clinical usefulness of plas-

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ma cytokines by analyzing their characteristic pattern of elevation throughout the whole course of radiotherapy in lung cancer patients who received radiotherapy with curative intent.

METHODS AND MATERIALS

1. Patient selection

In May 1998, we began a prospective study to determine the role of TGF-β1, TNF-α and IL-6 in the development of normal tissue injury after radiotherapy. Seventeen patients with lung cancer were enrolled (11 non-small cell lung cancer and 6 small cell lung cancer). Prior to patients accrual, all patients were informed of the exact purpose of this study and enrolled with formal consenting document. All patients underwent history taking and physical examination, radiographic evaluation for staging purposes (chest X-ray, bone scan and CT scans of the chest and upper abdomen). Histologic confirmation of malignancy was obtained by either bronchoscopic or CT-guided biopsy. Radiation was given at 1.8 Gy per fraction to isocenter, 1 fraction per day, 5 fraction per week for a total minimum dose of 54 Gy for SCLC and 60 Gy for NSCLC. Parallel opposing portals with individualized field were used for the initial 45 Gy. Target volume was primary mass with 2 cm margin plus whole mediastinum. When doses were reached up to 45 Gy, additional planning CT scans were obtained to avoid spinal cord from the limiting dose and to reduce and conform the target volume focusing on primary site and residual nodes.

Following the completion of radiotherapy, patients were evaluated at every 2 weeks for 4 months, then every one month until the end of this study. The endpoint of this study was marked when the patients developed symptomatic radiation pneumonitis occurring within 1~6 months after completion of radiotherapy or when 6 months passed after completion of radiotherapy without any clinical signs or symptoms of radiation-induced pneumonitis. High resolution computed tomographic scans (HRCT scans) were obtained when the patients developed pneumonitis symptoms and signs or when suggestive findings were detected on serial simple chest radiograms. Patients were considered to have developed radiation pneumonitis if they presented with one of the following category. 1) typical clinical symptoms like cough, fever and dyspnea, 2) infiltrative shadow on the simple chest radiogram, and 3) appearance of acute and chronic radiation change of lung parenchyme on HRCT scan. All patients having radiation-induced pulmonary symptoms were scored according to NCI scoring system, that is Grade 0 : No pulmonary symptoms due to radiation, Grade 1 : Pulmonary symptoms developed but not requiring steroids and/or oxygen, Grade 2 : Radiation-induced pulmonary symptoms requiring steroids, Grade 3 : Radiation-induced pulmonary symptoms requiring oxygen, and Grade 4 : Radiation induced pulmonary symptoms requiring intubation. A worsening of grade >1 was required to meet the diagnosis of "symptomatic pneumonitis".

2. Measurements of plasma cytokines

1) Sample collection

Peripheral blood samples were collected before, weekly during until the end of treatment and at each follow-up visit after completion of radiotherapy. If patients developed radiation pneumonitis, an additional blood sample was taken. The method for drawing blood and preparing plasma was designed to minimize platelet degranulation. The blood was collected into potassium contained tube. Sample was mixed by gentle inversion and immediately placed on a slurry of ice. Within 1 hr of collection, it was spun for 25 min at 3200 rpm in a refrigerated centrifuge at 4℃. The top two thirds of the plasma supernatant was withdrawn. The sample was stored at -70℃ until assay.

2) ELISA

Enzyme-linked immunosorbent assays (ELISAs) were performed to measure the plasma transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). The ELISAs for all of the cytokines employed quantitative "sandwich" techniques with antibodies specific for the cytokine of interest. Briefly, in all assays, standard and test samples were dispensed in duplicate into wells of 96-well microtiter plates, which had been pre-coated with monoclonal antibodies directed against the cytokines [anti-human IL-6 (Endogen, Woburn, MA), anti-human TNF-α (Endogen, Woburn, MA) and anti-TGF-β1 (R&D Systems, Minneapolis, Mn)]. Then, horseradish peroxidase-conjugated detection antibodies (biotinylated anti-human IL-6 (Endogen, Woburn, MA), TNF-α (Endogen, Woburn, MA) and TGF-β1 (R&D Systems, Minneapolis, Mn)) were added. After 1 hour of incubation, HRPO-conjugated streptavidin (Endogen, Woburn, MA) was added to the wells. The absorption at 450 nm was determined using an automated

ELISA microplate reader (Bio-Tek, EL312e, Winooski, VT).

The TGF-β1, TNF-α and IL-6 ratio were defined as the level at the end of treatment divided by pretreatment concentration.

3) Statistical analysis

For the same individuals, results before and after treatment were compared using the paired Student t-tests, whereas results comparing different groups were analyzed using independent t -test.

RESULTS

All patients were scored as having radiation induced pulmonary symptoms and their characteristics are listed in Table 1. The symptoms following radiation therapy developed around 4 weeks after completion of radiation therapy (range 0~20 weeks, median 4 weeks). Thirteen patients developed clinical pneumonitis, while four did not.

1. TGF-β1

Thirteen of 17 patients had elevated pre-radiotherapy level of TGF-β1. There was correlation between values of TGF-β1 for the pretreatment and 2~4 weeks completion of radiotherapy and the incidence of pneumonitis. For those who developed pneumonitis, the mean value of TGF-β1 at pretreatment was 38.45 ng/ml, while the values were 22.77 ng/ml in those without pneumonitis. It was statistically significant ($p<0.05$).

In the group of patients who did not develop pneumonitis, median TGF-β1 ratio was 0.225, which it was 1.38 in pneumonitis group. A TGF-β1 ratio of <1 indicates that the plasma TGF-β1 concentration at the end of radiotherapy was less than the pretreatment level (Fig. 1).

In eleven of 13 patients who developed pneumonitis, the pretreatment TGF-β1 level was elevated which declined subsequently during radiotherapy and then it elevated again to pretreatment levels or more within 2~4 weeks after completion of radiotherapy. For those who developed pneumonitis, the mean value of TGF-β1 at pretreatment was 38.45 ng/ml and elevated to 60.63 ng/ml within 2~4 weeks

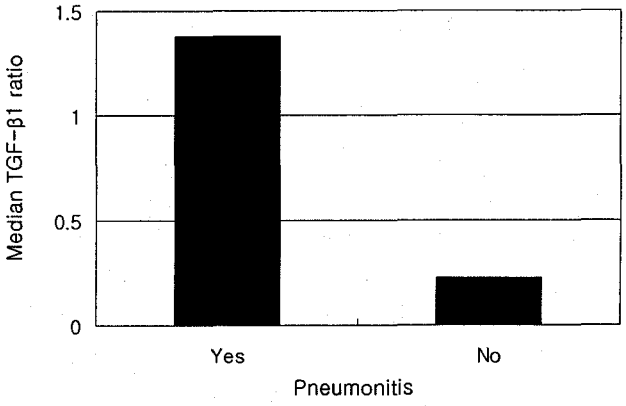

Fig. 1. Ratio of the plasma TGF-β1 in patients with and without pneumonitis.

Table 1. Summary of Patients Profile, Tumor Characteristics

No	Age	Sex	Treatment	Pathology	Stage	Dose (Gy)	Pneumonitis
P1	59	M	Operation	NSCLC	T2N2M0	5400	No
P2	69	M	Chemotx.	SCLC	limited	5400	No
P3	59	M	Chemotx	SCLC	limited	5400	No
P4	62	M	RT alone	NSCLC	T4N0M0	6600	No
P5	63	M	Chemotx	SCLC	limited	6300	Yes
P6	62	M	Chemotx	SCLC	limited	5400	Yes
P7	65	M	Chemotx	SCLC	limited	5400	Yes
P8	70	M	RT alone	NSCLC	T4N2M0	6480	Yes
P9	68	M	RT alone	NSCLC	T3N2M0	6480	Yes
P10	54	M	Chemotx	NSCLC	T4N1M0	6480	Yes
P11	57	M	Chemotx	SCLC	limited	5400	Yes
P12	56	M	RT alone	NSCLC	T4N2M0	6480	Yes
P13	60	M	RT alone	NSCLC	T4N3M0	6480	Yes
P14	36	F	Chemotx	NSCLC	T4N3M0	6120	Yes
P15	51	M	RT alone	NSCLC	T3N3M0	6480	Yes
P16	47	M	Operation	NSCLC	T2N1M0	5400	Yes
P17	54	M	RT alone	NSCLC	T3N2M0	6820	Yes

NSCLC : Non small cell lung cancer, SCLC : Small cell lung cancer, M : male, F : Female

after completion of radiotherapy. However the mean values TGF-β1 at pretreatment and 2~4 weeks after completion of radiotherapy were 22.77 ng/ml and 12.77 ng/ml respectively in those without pneumonitis. It was statistically significant (p<0.05, Fig. 2, 3).

2. TNF-α

In all patients, the TNF-α level was stable in pre-radiotherapy. At 2-4 weeks after completion of therapy, the levels were decreased in all patients regardless of developing pneumonitis. The value of TNF-α was relatively stable throughout the whole course of radiotherapy.

In patients who developed pneumonitis, the mean value of TNF-α at pretreatment and after completion of radiotherapy were 9.59 ng/ml and 9.80 ng/ml, but they were 5.27 ng/ml and 5.64 ng/ml in those without pneumonitis. There was no significant statistical difference and correlation between the value of TNF-α and the incidence of pneumonitis (p>0.05).

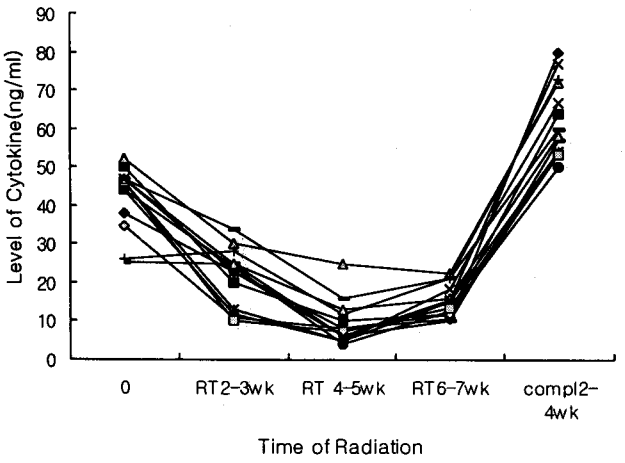

Fig. 2. TGF-β1 levels in patients with radiation pneumonitis.

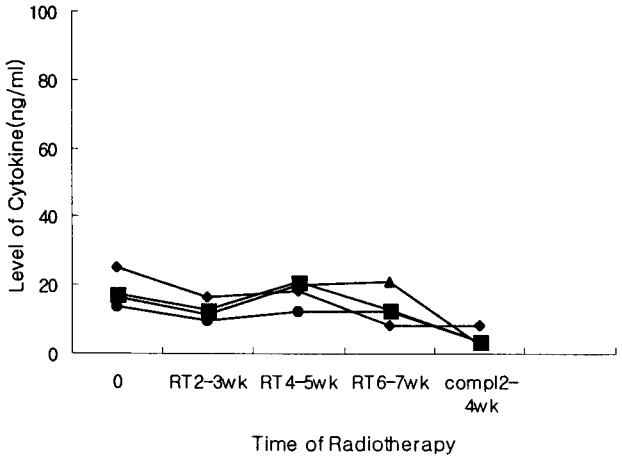

Fig. 3. TGF-β1 leves in patients without radiation pneumonitis.

3. IL-6

The pretreatment concentration of IL-6 was increased in patients who developed pneumonitis (mean value, 13.84 ng/ml) compared to those who did not (mean value, 10.95 ng/ml). For the pneumonitis patients, this level was decreased slightly in 2~4 weeks after completion of radiotherapy (mean value, 13.22 ng/ml). In pneumonitis group, IL-6 was slightly elevated at pretreatment plasma which had shown continuous elevation during radiotherapy then decreased within 2~4 weeks after completion of therapy. In patients without pneumonitis, the value was not elevated during treatment and within 2~4 weeks after completion of radiotherapy, on the contrary, it was decreased to pretreatment level in all non-pneumonitis patients. But this was not statistically significant (p>0.05).

4. HRCT findings in pneumonitis patients

Twelve of the 13 patients who developed pneumonitis had shown a marked change on HRCT scan. These findings were patchy, confluent regions of increased pulmonary attenuation. HRCT findings were well correlated with pneumonitis symptoms.

DISCUSSION

Even though the lower respiratory tract can tolerate moderate doses of radiation, the lung itself is the major dose-limiting structure and highly radiosensitive organ in thoracic cage. Radiation injury on the lung has been classified as either early radiation pneumonitis or late radiation fibrosis. Early radiation-induced damage is mainly due to vascular injury to small vessels and capillaries resulting in vascular congestion and increased capillary permeability. When the vascular injury becomes severe and chronic, arteriocapillary fibrosis develops. This changes of fibrosis in the lung is an active process involving the production of a number of inflammatory and fibrogenic cytokines by various cell systems like macrophages, epithelial cells, pneumocytes and fibroblasts.[9~12] The published studies so far have clearly indicated that in the cellular events, the fibrosis is a complex process related with the overproduction and deposition of col-

lagens, fibronectin and other extracellular matrix proteins. In terms of molecular level, this fibrotic tissue remodelling results from the overproduction of fibrogenic cytokines.[6, 9] Several cytokines, notably interleukins (IL-1, IL-6, IL-8), tumor necrosis factor alpha (TNF-α), transforming growth factor beta1 (TGF-β1) and platelet derived growth factor (PDGF) have been defined to modulate the growth and secretion of fibroblasts.[5, 6, 13, 14] Among these fibrogenic cytokines, with respect to radiation-induced lung injury, TGF-β1 in particular has been identified as key mediator of the cellular processes underlying the induction of the fibrotic response.[9, 11] Recently published clinical work describes a significant rise in plasma TGF-β1 levels during radiotherapy, which could be correlated with the risk of symptomatic radiation-induced pneumonitis. Anscher et al reported, in thirty-six patients who received radiation therapy on the thorax with curative intent for lung cancer, Hodgkin's disease and thymoma, thirteen patients developed pneumonitis.[1, 15] According to their results, the patients who developed symptomatic pneumonitis differed from those who did not with respect to the pattern of change in their plasma TGF-β1 concentration over the course of radiotherapy. They concluded for those patients who did not develop symptomatic pneumonitis, plasma TGF-β1 concentration tended to normalize to pretreatment level at the completion of radiotherapy but in patients who did experience this complication, the level remained elevated until the end of radiotherapy.[16] Other authors confirmed this result and our data was also very much compatible with them (Fig. 2 and 3). For the pneumonitis group, the pretreatment or baseline concentrations of TGF-β1 were notably elevated compared to the non-pneumonitis group. There was a characteristic pattern of elevation for the pneumonitis group, that is, from the beginning of radiotherapy the elevated concentration of TGF-β1 started to decrease and reached the bottom level in 4-5 weeks and gradually increased again and remained elevated in several weeks even after completion of radiotherapy. This pattern of elevation could not be identified in non-pneumonitis group (Fig. 2). On the contrary, for the non-pneumonitis group, the TGF-β1 concentration was remained stable over the whole course of radiotherapy. Even in several weeks after completion of radiotherapy, this pattern was not changed for the non-pneumonitis group. This pattern of change in plasma TGF-β1 levels from our data may be useful to define patients at high or low risk for radiation pneumonitis. Because TGF-β1 not only promotes fibrogenesis, but also has local inflammatory properties, it may not be questionable that elevated level of TGF-β1 at the beginning of radiotherapy indicates the acute inflammatory responses in the early phases of radiation injury. But according to the some recent investigations, in cancer patients, the stromal cells associated with tumors have a tendency of increased production of TGF-β1 by themselves.[17, 18] So it may be very confusing whether the initial elevation of circulating TGF-β1 reflects mainly self-production by tumors or acute inflammatory response triggered by radiotherapy. Since the present study and previous works done by other investigators demonstrates that circulating TGF-β1 levels are decreasing by thoracic irradiation (whether it was elevated or not at the beginning of radiotherapy), it can be assumed that additional TGF-β1 production as a result of irradiation does not get into circulation but rather is activated and/or degraded at the site of production.[18] Therefore it can be suggested that some tumors directly contribute to the enhanced risk of normal tissue injury by radiotherapy via production of excess TGF-β1, which can be detected in the circulation.

Since Rubin and colleagues suggested the hypothesis of "cascade of cytokines" beginning at the time of radiation,[9] TNF-α has been also regarded as one of the key cytokines involved in mediating pulmonary damage.[19, 20] TNF-α, first found in the sera of mice treated with Bacillus Calmette-Guerin and endotoxin, have a wide range of biological activities including stimulation of fibroblast growth. In association with pulmonary injury by radiation, some investigators suggested TNF-α is a major factor causing pulmonary fibrosis because activated human alveolar macrophage, either by radiation or inhaled foreign particles, have more capacity than blood monocyte to produce TNF-α.[7, 21] Piguet et al, by experimental infusion of TNF-α in vitro and in vivo, demonstrated that TNF-α reproduced many of the events observed during fibrosis and was induced in larger amounts than other fibrogenic cytokines.[20] Sherman and colleagues reported an increase in TNF-α mRNA in human peripheral blood monocyte after irradiation with doses as low as 2 Gy.[22] However, little has been investigated yet about the role of TNF-α to identify those patients who will be at risk of developing radiation-induced pneumonitis. In the present study, we found that the mean value of TNF-α in pneumonitis group was higher than non-pneumonitis group before and after radiation but there wasn't any notable pattern of

elevation in pneumonitis group. Furthermore, because the elevated mean value in the pneumonitis group didn't show any statistical significance due to individual bias, we concluded it is not recommendable to use the measurement of TNF-α in dentifying risk group of radiation-induced pneumonitis. The possible explanation for this result is TNF-α, unlike TGF-β1, though it contributes to mediate the inflammatory lung injury caused by radiation, the amount of individual production of TNF-α by tumor itself was not enough to be detected in the peripheral blood to distinct high and low risk group. To confirm this theory, we are planning to accrue more patients in the next study to exclude the individual bias.

IL-6 is another cytokine of interests in the complicated process of "cytokine cascades" caused by radiation. It is regarded as an important regulator of inflammation and immunity and also believed to be produced by activated monocytes as well as fibroblast and T-cells.[8] According to the recently published literature, IL-6 is mainly stimulated and induced by the IL-1, TNF-α in the proinflammatory procedure resulting fibrosis.[8, 22, 23] But, until now, the exact role of IL-6 in developing pneumonitis has not been clearly demonstrated. In the present study, we measured plasma concentration of IL-6 as a package work with TGF-β1 and TNF-α to demonstrate any possible role in association with developing pneumonitis, but the result we obtained was very similar with that of TNF-α. Though the level of IL-6 in pre- and post-radiation time was higher in the pneumonitis group like TNF-α, there wasn't any striking difference in both groups. There is also some other possible explanations for this result, but considering the fact that the synthesis of IL-6 is mainly contributed by the TNF-α, it is hard to find any clue of IL-6 in association with radiation-induced pneumonitis as long as the measurement of TNF-α has not shown any statistical significance.

CONCLUSION

Since the present study indicates the characteristic pattern of elevation of TGF-β1 in pneumonitis group, the measurements of serial plasma TGF-β1 may be especially useful to identify high or low risk patients who would experience symptomatic radiation pneumonitis, but it should be strictly confined to the subset of patients in whom the TGF-β1 is increased at baseline. By identifying high and low risk group in lung cancer patients, this serial measurements of TGF-β1 can be also useful to select those patients who would be candidates for the dose escalation trials, because it is those patients at low risk for symptomatic pneumonitis whom one would like to select for such dose escalation studies.

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국문 초록

폐암환자에서 방사선 폐렴 예측을 위한 혈장 Cytokine 측정

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목 적 : 폐암으로 확진되어 근치적 방사선 치료를 받은 환자에서 방사선폐렴이 발생할 수 있는 위험군을 사전에 예측해 보고자 혈장내 TGF-β1, TNF-α, IL-6의 농도를 측정하여 폐렴 발생과의 상관관계를 분석하고자 하였다.

재료 및 방법 : 1998년 5월부터 1999년 7월까지 폐암으로 확진되어 근치적 방사선 치료를 받은 17명의 환자(비소세포암 11명, 소세포암 6명)을 대상으로 하였다. 방사선 치료는 주 5회 매일 1.8 Gy씩 실시하였고 비소세포암과 소세포암에서 각각 평균 60 Gy와 54 Gy를 조사하였다. 모든 환자에서 방사선치료 전, 방사선치료 중 주 1회, 치료 후 추적관찰로 내원시마다 혈액을 채취하여 혈장 TGF-β1, TNF-α 및 IL-6의 양을 ELISA법으로 측정하였다. 모든 환자에서 단순흉부촬영(치료중 주1회, 치료 후 추적관찰 시마다 촬영) 및 방사선 폐렴과 연관된 증세를 관찰하여 방사선 폐렴의 징후가 발견되면 즉시 고해상도 컴퓨터 단층 촬영(HRCT)를 촬영하여 방사선 폐렴 발생여부를 확진하고자 하였다.

결 과 : 17명의 환자 중 13명에서 방사선 폐렴과 연관된 증세가 발현되었고 단순 흉부 촬영과 고해상도 컴퓨터 단층 촬영에서 이를 확인할 수 있었다. 방사선 폐렴이 발생한 환자에서 측정한 TGF-β1의 경우 특징적인 수치 변화를 보여 치료 전 평균값은 38.45 ng/ml로 방사선 폐렴이 발생하지 않은 군에 비해 상승되어 나타났고(22.77 ng/ml) 방사선치료 중 13.66 ng/ml의 평균값을 보인 후 다시 점진적으로 상승하여 치료 2~4주 후까지 평균 60.63 ng/ml로 상승되어 유지되었고 이 수치는 폐렴이 발생하지 않은 군과 비교할 때(12.77 ng/ml) 통계적으로 의미가 있었다($p<0.05$). TNF-α와 IL-6의 수치도 방사선 폐렴군에서 더 높게 측정되었으나 수치변화의 양상은 특징적이지 못하였으며 통계학적 의미도 찾을 수 없었다.

결 론 : 방사선 치료를 받은 폐암환자에서 치료 전과 치료 기간 중 및 치료 후 측정한 혈장 TGF-β1,의 수치는 향후 방사선 폐렴이 발생할 위험군을 예측할 수 있는 지표로 사용할 수 있을 것으로 사료된다.

핵심용어 : 폐암, 방사선치료, 방사선폐렴, 사이토카인