Serum Levels of Cytokines in Patients with Untreated Primary Lung Cancer

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ABSTRACT

To evaluate the relationships between serum endogenous cytokine levels and their clinical implications in cancer patients, we measured the serum levels of endogenous granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), and interleukin 6 (IL-6) in patients with untreated primary lung cancer. The serum G-CSF level was measured using a chemiluminescent ELISA, and the other cytokine levels were measured using ELISA. Fifty healthy adults and 183 patients with primary lung cancer were studied. The mean M-CSF level in the lung cancer patients (1106.4 units/ml) was significantly higher than that in the healthy adults (836 units/ml, P = 0.0001). In patients with large cell carcinoma, endogenous G-CSF, M-CSF, and IL-6 levels were significantly higher than those in patients with carcinomas of other cell types (P < 0.05). Univariate analysis showed that survival of 159 non-small cell lung cancer patients with high (more than cutoff level) G-CSF, M-CSF, and IL-6 levels was significantly poorer than that of patients with low levels (Wilcoxon’s test, P = 0.018, P < 0.0001, and P < 0.0001, respectively). Survival of patients with high levels of two or more cytokines was poorer than that of those with high levels of one cytokine or normal cytokine levels (P < 0.0001). Multivariate analysis using Cox’s proportional hazards model showed that high M-CSF and C-reactive protein levels correlated significantly with poor survival (P = 0.037 and 0.037, respectively). Our preliminary data suggest that high M-CSF levels in nonsmall cell lung cancer may be of poor prognostic value.

INTRODUCTION

Many reports of the production of various cytokines by malignant neoplasms have been published. The types of tumor reported to produce cytokines include hematological malignancies (1-5) and solid tumors (6-10). There are several case reports of primary lung cancers that appeared to produce various cytokines such as G-CSF, GM-CSF, M-CSF, or IL-6, and such production probably causes leukocytosis (11-14). In most of these studies, the tumor cells were cultured in vitro, or cell lines derived from the tumors were investigated. The roles of cytokines in relation to the tumor progression have been studied using in vitro models. Evidence of a correlation between GM-CSF gene expression in tumor cells and lung metastases in a murine model was obtained (15), and IL-6 cDNA-transfected lung carcinoma cells shortened survival in mice (16). CSF activity has been demonstrated in tumor-conditioned medium and found to parallel the activity in patients’ sera (11-13).

In this study, we measured serum G-CSF, GM-CSF, M-CSF, and IL-6 levels in patients with untreated primary lung cancer and investigated the relationships between the disease manifestations and serum cytokine levels.

PATIENTS AND METHODS

Patients. Serum samples were collected from patients with previously untreated primary lung cancer and normal volunteers and stored at −80°C. Each patient underwent routine staging in accordance with the UICC criteria (17); history and physical examination; complete blood counts; serum chemistry; serum tumor markers; chest X-ray; computed tomography of the brain, chest, and abdomen; abdominal echography; and bone scanning. Patients with evidence of microbiologically proven infection were excluded. All of the patients provided informed consent in accordance with institutional guidelines.

Serum Cytokines. Serum G-CSF levels were quantitated by a CELISA (Chugai Pharmaceutical Co. Ltd., Tokyo, Japan; Ref. 18), and serum GM-CSF, M-CSF, and IL-6 levels were measured using ELISAs (Genzyme, Cambridge, MA; Midorijuji Pharmaceutical Co. Ltd., Tokyo, Japan; and R&G Systems, Minneapolis, MN, respectively) according to the manufacturers’ instructions. The lower limits of sensitivity for these assays were: 10 pg/ml for G-CSF, 4 pg/ml for GM-CSF, 10 units/ml for M-CSF, and 0.35 pg/ml for IL-6. We were able to obtain higher sensitivity using the CELISA (the lower limit is 10 pg/ml) for G-CSF measurement than with the conventional ELISA, of which the lower limit of sensitivity is 30 pg/ml. The intraassay

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3 The abbreviations used are: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage CSF; M-CSF, macrophage CSF; IL-6, interleukin 6; CELISA, chemiluminescent ELISA; CRP, C-reactive protein; ANC, absolute neutrophil count; Hb, hemoglobin; CI, confidence interval.
coefficients of variation obtained from 10 repeated assays of three sera ranged from 3.8 to 4.6%, and the interassay coefficients of variation of assays of three sera conducted on 10 working days ranged from 4.7 to 4.9%.

**Statistical Analysis.** The significance of differences between the mean endogenous cytokine levels in different subsets of patients was determined using the Student two-tailed unpaired t test and one-way ANOVA followed by Dunnet and Duncan’s multiple range test. Correlation coefficients between the different parameters were calculated using the Spearman rank sum test, and categorical data were compared using the χ² test (19). Survival curves were computed using the method of Kaplan and Meier (20), and differences between survival of subgroups of patients were compared using the generalized Wilcoxon test. The Cox proportional hazards regression model (21) was used to determine the joint effects of several variables on survival. Differences at P < 0.05 were considered to be significant. Statistical analysis was performed using Stat View 4.11 (Abacus Concepts, Inc., Berkeley, CA).

### RESULTS

Samples from 183 consecutive patients (mean age, 65 years) diagnosed as having primary lung cancer between November 1992 and July 1993 and 50 serum samples from healthy adults (mean age, 63 years) were collected in the National Cancer Center Hospital. The patients’ characteristics are shown in Table 1.

### Circulating Levels of Cytokines. The test results are shown in Fig. 1. The mean G-CSF level of the patients with lung cancer was 16.5 (range, 1–380) pg/ml and that of the healthy adults was 12.9 (range, 5–53) pg/ml. The cutoff level to reach the mean value plus twice the SD would be 30.2 pg/ml, and 11 (6.0%) of the 183 patients had high levels (beyond the cutoff level). The mean GM-CSF level of the patients was 10.5 (range, 6.4–22.6) pg/ml and that of the healthy adults was 9.6 (range, 6.6–17.0) pg/ml. The cutoff level would be 14.2 pg/ml, and 9 (4.9%) of the patients had high levels. The mean M-CSF level of the patients was 110.6 (range, 514–2475) units/ml and that of the healthy adults was 813.9 (range, 487–1470) units/ml. The

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**Table 1** Characteristics of the patients and cytokine concentrations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of subjects</th>
<th>G-CSF</th>
<th>GM-CSF</th>
<th>M-CSF</th>
<th>IL-6</th>
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<tr>
<td>Healthy adults</td>
<td>50</td>
<td>12.9 ± 8.7</td>
<td>9.6 ± 2.3</td>
<td>813.9 ± 184.8</td>
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<tr>
<td>&lt;60</td>
<td>60</td>
<td>23.4 ± 49.1ab</td>
<td>9.9 ± 2.2</td>
<td>1091.0 ± 510.4a</td>
<td>11.4 ± 28.0</td>
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<tr>
<td>≥60</td>
<td>123</td>
<td>13.2 ± 9.6</td>
<td>10.8 ± 2.8</td>
<td>1113.9 ± 339.4a</td>
<td>9.7 ± 36.9</td>
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<tr>
<td>Male</td>
<td>130</td>
<td>17.3 ± 34.2</td>
<td>10.6 ± 2.2</td>
<td>1138.7 ± 424.3a</td>
<td>12.9 ± 40.1a</td>
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<tr>
<td>Female</td>
<td>53</td>
<td>14.6 ± 11.6</td>
<td>10.2 ± 3.5</td>
<td>1027.2 ± 352.5a</td>
<td>3.9 ± 6.9</td>
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<tr>
<td>0</td>
<td>53</td>
<td>12.5 ± 5.2</td>
<td>10.1 ± 2.3</td>
<td>978.8 ± 367.3a</td>
<td>3.5 ± 6.0</td>
</tr>
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<td>1</td>
<td>95</td>
<td>19.8 ± 40.1</td>
<td>10.2 ± 2.4</td>
<td>1131.9 ± 397.8a</td>
<td>14.1 ± 45.8a</td>
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<tr>
<td>2</td>
<td>29</td>
<td>13.7 ± 9.5</td>
<td>11.3 ± 3.6</td>
<td>1210.0 ± 401.8a</td>
<td>8.0 ± 14.1</td>
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<td>3</td>
<td>3</td>
<td>19.3 ± 12.7</td>
<td>11.3 ± 1.6</td>
<td>1317.7 ± 586.3a</td>
<td>23.0 ± 31.3a</td>
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<tr>
<td>4</td>
<td>2</td>
<td>10.0 ± 4.2</td>
<td>7.4 ± 2.2</td>
<td>1568.0 ± 705.7a</td>
<td>27.8 ± 35.3a</td>
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<td>Adenocarcinoma</td>
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<td>10.3 ± 3.0</td>
<td>1022.5 ± 339.1a</td>
<td>7.8 ± 40.6</td>
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<td>Squamous cell</td>
<td>51</td>
<td>16.0 ± 11.9</td>
<td>11.2 ± 2.5</td>
<td>1147.5 ± 367.8a</td>
<td>8.1 ± 18.4</td>
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<td>Large cell</td>
<td>7</td>
<td>98.0 ± 126.6ab</td>
<td>10.4 ± 1.5</td>
<td>1892.4 ± 616.5ab</td>
<td>67.9 ± 51.7ab</td>
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<tr>
<td>Small cell</td>
<td>24</td>
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<td>10.6 ± 1.6</td>
<td>1039.7 ± 369.6a</td>
<td>6.9 ± 13.7</td>
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<tr>
<td>Others</td>
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<td>12.3 ± 3.6</td>
<td>8.6 ± 0.5</td>
<td>1259.3 ± 409.9a</td>
<td>11.3 ± 17.0</td>
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<tr>
<td>I</td>
<td>44</td>
<td>11.4 ± 5.8</td>
<td>9.6 ± 2.1</td>
<td>931.2 ± 227.4a</td>
<td>1.37 ± 3.6</td>
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<tr>
<td>II</td>
<td>13</td>
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<td>10.5 ± 1.9</td>
<td>1132.8 ± 422.7a</td>
<td>5.0 ± 10.6</td>
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<tr>
<td>IIIa</td>
<td>37</td>
<td>14.0 ± 7.9</td>
<td>11.8 ± 3.2</td>
<td>1110.0 ± 383.9a</td>
<td>5.9 ± 7.7</td>
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<tr>
<td>IIIb</td>
<td>28</td>
<td>14.0 ± 11.2</td>
<td>11.7 ± 3.3</td>
<td>1076.3 ± 402.2a</td>
<td>5.1 ± 7.3</td>
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<td>1238.3 ± 466.4a</td>
<td>22.8 ± 56.7a</td>
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<td>T1</td>
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<td>9.8 ± 2.6</td>
<td>916.8 ± 215.5a</td>
<td>2.2 ± 5.3</td>
</tr>
<tr>
<td>T2</td>
<td>70</td>
<td>20.5 ± 45.2</td>
<td>10.6 ± 2.6</td>
<td>1159.1 ± 441.5a</td>
<td>10.9 ± 28.6</td>
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<td>T3</td>
<td>31</td>
<td>14.2 ± 8.2</td>
<td>10.54 ± 0.9</td>
<td>1051.2 ± 295.1a</td>
<td>19.1 ± 68.6a</td>
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<td>T4</td>
<td>42</td>
<td>17.3 ± 16.5</td>
<td>11.0 ± 3.2</td>
<td>1239.9 ± 470.8a</td>
<td>10.4 ± 14.6</td>
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<tr>
<td>N0</td>
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<td>11.5 ± 5.8</td>
<td>10.0 ± 2.6</td>
<td>934.6 ± 235.2a</td>
<td>2.1 ± 3.2</td>
</tr>
<tr>
<td>N1</td>
<td>37</td>
<td>18.8 ± 17.8</td>
<td>10.6 ± 2.6</td>
<td>1093.7 ± 387.5a</td>
<td>7.5 ± 12.7</td>
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<tr>
<td>N2</td>
<td>61</td>
<td>21.9 ± 48.2</td>
<td>11.0 ± 2.7</td>
<td>1238.9 ± 474.4a</td>
<td>18.7 ± 53.2a</td>
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<tr>
<td>N3</td>
<td>23</td>
<td>12.4 ± 7.4</td>
<td>10.9 ± 2.9</td>
<td>1238.5 ± 418.5a</td>
<td>14.5 ± 35.3</td>
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</table>

*Significantly different from healthy adults by one-way ANOVA followed by Dunnet’s multiple range test (P < 0.05).

*Significantly different from the other values by Duncan’s multiple range test (P < 0.05).
cutoff level would be 1183.5 units/ml, and 60 (32.8%) of the patients had high levels. The mean IL-6 level of the patients was 10.3 (range, 0.3–384.7) pg/ml and that of the healthy adults was 1.3 (range, 0.3–22.5) pg/ml. The cutoff level would be 8.4 pg/ml, and 37 (20.2%) of the patients had high levels. Statistical analysis (using Student's t test) revealed that the M-CSF levels were significantly higher in lung cancer patients than in healthy adults (P = 0.0001).
Table 2  Relationship between cytokines and various parameters\textsuperscript{a}  
\begin{tabular}{|c|c|c|c|c|}
\hline
 & G-CSF & GM-CSF & M-CSF & IL-6 \\
\hline
WBC & $r = 0.274$ & $r = 0.177$ & $r = 0.315$ & $r = 0.270$ \\
 & $P = 0.0004$ & $P = 0.0847$ & $P < 0.0001$ & $P = 0.0004$ \\
\hline
ANC & $r = 0.275$ & $r = 0.146$ & $r = 0.312$ & $r = 0.234$ \\
 & $P = 0.0004$ & $P = 0.0572$ & $P < 0.0001$ & $P = 0.0023$ \\
\hline
Hb & $r = -0.287$ & $r = 0.065$ & $r = -0.321$ & $r = -0.323$ \\
 & $P = 0.9316$ & $P = 0.4015$ & $P < 0.0001$ & $P < 0.0001$ \\
\hline
PLT & $r = 0.206$ & $r = 0.075$ & $r = 0.128$ & $r = 0.290$ \\
 & $P = 0.0079$ & $P = 0.3294$ & $P = 0.0976$ & $P = 0.0002$ \\
\hline
CRP & $r = 0.261$ & $r = 0.133$ & $r = 0.562$ & $r = 0.431$ \\
 & $P = 0.0088$ & $P = 0.0891$ & $P < 0.0001$ & $P < 0.0001$ \\
\hline
\end{tabular}

\textsuperscript{a} Variables are Spearman correlation coefficients. Negative values signify inverse correlations, while positive values demonstrate direct correlations. The value of the coefficient signifies the strength of the correlations with $+1$ or $-1$ as the maximum value.

\textsuperscript{b} PLT, platelet count.

### Relationships between Cytokine Levels and Laboratory Parameters.

The G-CSF levels correlated weakly with the WBC counts, ANC, platelet counts, and serum CRP levels (Table 2). The GM-CSF levels correlated with no laboratory parameters. The M-CSF levels correlated with the serum CRP levels (Spearman rank sum correlation coefficient, $r = 0.562$, $P < 0.0001$) and correlated weakly with the WBC count, ANC, and Hb count. The IL-6 levels correlated with the serum CRP levels ($r = 0.431$, $P < 0.0001$) and correlated weakly with the WBC count, ANC, Hb count, and platelet count. The serum levels of some tumor markers, namely, carcinoembryonic, carbohydrate 19-9, carbohydrate 125, neuron-specific enolase antigens, and sialylated stage-specific embryonic antigen 1 (SLX), and those of lactate dehydrogenase did not correlate with any cytokine level.

### Relationships between Cytokine Levels and Patients’ Characteristics.

The G-CSF levels were significantly higher in lung cancer patients below 60 years of age than in the healthy adults and patients aged 60 or over ($P < 0.05$; Table 1). In patients with large cell carcinoma, the G-CSF, M-CSF, and IL-6 levels were significantly higher than in those with carcinomas of other cell types ($P < 0.05$). There were no differences among GM-CSF levels. The M-CSF levels were significantly higher in patients in all of the subcategories, except stage I, T\textsubscript{1}, and N\textsubscript{0}, than in the healthy adults. The IL-6 levels were significantly higher in male P\textsubscript{S} 1, 3, and 4, stage IV, and T\textsubscript{4} stage patients than in healthy adults ($P < 0.05$).

The distributions of cytokine combinations in patients with high cytokine levels are shown in Table 3. Forty percent (73/183) of the patients had a high level of at least one cytokine, and 48% (35/73) of these had high levels of two or more.

We investigated the relationships between cytokine levels and metastatic sites in patients with stage IV disease. Metastasis to the adrenal gland was significantly more frequent in patients with high than low G-CSF levels (4/6 versus 4/55; $P < 0.0001$), but no correlations between the other cytokines and metastatic sites were found.

### Prognostic Value of Clinicopathological Characteristics.

To evaluate the relationships between serum cytokine levels and prognosis, we performed univariate analysis of 159 patients with non-small cell lung cancer using the generalized Wilcoxon test (Table 4). The serum G-CSF, M-CSF, and IL-6 levels were demonstrated to be poor prognostic variables. Survival was poorer in the group with high levels of two or more cytokines than that in the group with high levels of one cytokine or normal cytokine levels ($P < 0.0001$). The survival curve is shown in Fig. 2. Univariate analysis using the Cox proportional hazards model also demonstrated that the serum G-CSF, M-CSF, and IL-6 levels as a continuous variable were significant prognostic values ($P = 0.0004$, risk ratio $= 1.009$, 95% CI $= 1.004-1.014$; $P < 0.0001$, risk ratio $= 1.002$, 95% CI $= 1.001-1.002$; $P < 0.0001$, risk ratio $= 1.009$, 95% CI $= 1.005-1.013$, respectively). Multivariate analysis using the Cox proportional hazards model is shown in Table 5. Two variables, serum M-CSF ($P = 0.037$) and serum CRP ($P = 0.037$) levels, were found to be significant predictors of poor survival. The Kaplan-Meier survival curve according to serum M-CSF levels is shown in Fig. 3.

### DISCUSSION

Recently, various cytokines that stimulate hematopoiesis have been identified using a structural approach, and each cDNA has been cloned. Furthermore, it became possible to measure cytokine levels using the ELISA. In the present study, we measured serum G-CSF, GM-CSF, M-CSF, and IL-6 levels in lung cancer patients using the ELISA. The M-CSF level was significantly higher in lung cancer patients than healthy subjects (Fig. 1). Although the G-CSF and IL-6 levels were not significantly higher than those in the healthy subjects, several patients had extremely high levels. The hypothesis that lung cancer cells produce certain cytokines has been confirmed, a lung tumor-producing CSF was first reported by Asano et al. (22), and, subsequently, several other tumors were reported to do so (12, 13, 22–26). Cytokine production by lung cancer may contribute to leukocytosis (12–14). However, the biological aspects and clinical manifestations of the relationships between cytokines and lung cancer are not well understood.

Most of the patients with high cytokine levels had high levels of two or more cytokines (Table 2), and their survival was poorer than that of the other patients. Expression of G-CSF and IL-6 genes has been demonstrated in a lung cancer cell line (23), and the production of multiple cytokines in lung cancer patients may be related to their poor prognosis.

Most of the cytokine-producing lung cancers previously reported were large cell or poorly differentiated carcinomas...
(11-14). Large cell carcinoma is defined as an undifferentiated carcinoma without the characteristic features of squamous cell, small cell, or adenocarcinomas defined in the WHO classification (27). Large cell carcinomas grow rapidly and are usually quite large by the time they are diagnosed, and the associated prognosis appeared to be poor (28). Some investigators have attributed leukocytosis to CSF production by large cell cancers.

Our data showed that the mean G-CSF, M-CSF, and IL-6 levels were significantly higher in large cell carcinoma patients than in those with other types of cancer, and we found rapidly growing tumors in patients with extremely high cytokine levels. Therefore, these cytokines may contribute to the progressive nature of large cell bronchogenic carcinoma.

Some authors indicated there may be a correlation between the cytokines produced by tumor cells and the tumor specificity of metastasis (15, 29, 30). Rikiishi et al. (31) suggested that the expression and adhesive potential of adhesion protein may be regulated by a certain cytokine excreted by the tumor cells. Our results with stage IV lung cancer patients revealed that high G-CSF levels were correlated with adrenal metastasis, which suggests that cytokines may play certain roles in tumor growth and metastasis.

Activated monocytes or macrophages, T and B cells, fibroblasts, endothelial cells, and a variety of tumor cells have been shown to produce IL-6 (32). Several lines of evidence imply a pathogenic role for IL-6 in some lymphoid malignancies. The circulating IL-6 level has been suggested to be an important prognostic factor of multiple myeloma (33) and malignant lymphoma (1, 3). Our data showed that IL-6 levels correlated with T<sub>x</sub>, N<sub>x</sub>, and stage IV disease, and these observation indicate that IL-6 may be involved in tumor growth.

A wide variety of mesenchymal and epithelial tissues elaborate M-CSF, the blood levels of which are normally regulated by the total-body macrophage count. Production of M-CSF by ovarian cancer cells (34) and hematological malignancies has been observed. Yamada et al. (35) stated that plasma M-CSF levels reflected the disease activity of adult T-cell leukemia. Our data demonstrated that high serum M-CSF levels may be significant markers of poor prognosis in patients with non-small cell lung cancer.

Correlations between documented infections and elevated levels of these cytokines have been demonstrated (36-39), and the G-CSF and IL-6 levels were higher in patients with atypical pneumonia than in normal subjects (40). Since the source of these elevated cytokine levels has not been determined, it should be confirmed whether tumors can produce them.

Serum levels of cytokines may play a critical role in the prognosis of patients with large cell carcinoma of the lung.
Fig. 2 Survival of 159 patients with non-small cell lung cancer according to number of cytokines of high levels: 0 (n = 91), 1 (n = 36), 2 (n = 22), and 3 (n = 10). P value was determined using the generalized Wilcoxon test.

Fig. 3 Survival of 159 patients with non-small cell lung cancer according to serum M-CSF levels. P value was determined using the generalized Wilcoxon test.

However, our data are preliminary because of relatively short follow-up time, and suggest the clinical outcome of patients with non-small cell lung carcinoma and high M-CSF levels may be poor and may give new insight into treatment of lung cancer associated with high cytokine levels. Therefore, additional studies are warranted to identify the biological roles of cytokines in the pathogenesis or progression of lung cancer.

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