Prognostic Value of Serial Serum Interleukin-6 Level Estimation in Patients with Lung Cancer: A Preliminary Report

Arleta Wojciechowska-Lacka\textsuperscript{b}, Ewa Adamiak\textsuperscript{b}, Grazyna Stryczynska\textsuperscript{b} and Jan K. Lacki\textsuperscript{a}

\textsuperscript{b}Department of Radiotherapy, Wielkopolska Cancer Center, Poznan, Poland, and \textsuperscript{a}Department of Clinical Immunology and Allergy, K. Marcinkowski University of Medical Sciences, Poznan, Poland

(Received July 11, 1996; returned for revision January 27, 1997; accepted May 15, 1997)

In the present report, we serially measured the levels of interleukin-6 (IL-6) and some acute-phase proteins (APP) in 61 lung cancer patients undergoing radiotherapy in order to investigate the relationship between the response to the treatment and the changes in parameters of systemic inflammatory response.

The patients were divided into two groups depending on the response to the treatment. The first group (referred to as responders) comprised 32 patients with stable disease, partial remission or total remission. Twenty-nine patients with progression of the disease were included to the second group (referred to as non-responders). Six patients died due to the lung cancer during the study. We showed a decrease in IL-6 serum level and C-reactive protein (CRP) level in responders but not in non-responders. However, the most interesting results were obtained after retrospective analysis of the data of six deceased patients. In these patients we observed an elevation of IL-6 and CRP before the patients' deaths.

Following the changes in acute-phase response and interleukin-6 serum levels in lung cancer patients seems to be helpful in prognosis of the outcome of the disease. Based on our data, we conclude that an elevation in IL-6 and/or CRP level in patients with lung cancer may serve as an adverse prognostic factor.

INTRODUCTION

Acute-phase proteins (APP)\textsuperscript{c} have been defined as those which plasma concentration increases (positive APP) or decreases (negative APP) by 25 percent or more following tissue injury or infection. Changes in APP are observed in inflammatory and autoimmune diseases as well as in cancer. APPs are mainly synthesized and glycosylated by the liver. Although at present, nine cytokines have been found capable of directly inducing acute-phase proteins' production in the liver (i.e., IL-1, IL-6, IL-11, TNF [tumor necrosis factor], interferon-gamma, LIF [leukemia inhibitory factor], TGF-beta [transforming growth factor-beta], oncostatin M and CNTF [ciliary neurotrophic factor] [1-4]), IL-6 is a major hepatocyte stimulator of APP synthesis [1, 5].

Interleukin-6 (IL-6) is a potent multifunctional protein. It is produced by many different cell types including T-cells, B-cells, monocytes, fibroblasts, chondrocytes, mesangial cells, glial cells, endothelial cells, keratinocytes and certain tumor cells [1, 6]. However, monocytes/macrophages are predominantly responsible for IL-6 production. IL-6 is considered to be a cytokine that plays a central role in the host-defense mechanism. The biological activities of IL-6 have been shown to take part in the induction of

\textsuperscript{a} To whom all correspondence should be addressed: Jan K. Lacki, M.D., Department of Clinical Immunology and Allergy, K. Marcinkowski University of Medical Sciences, ul. Winogrady 144, PL-61-626 Poznan, Poland. Tel: 48-61-528802; Fax: 48-61-524261.

\textsuperscript{c} Abbreviations: APP, acute-phase proteins; CRP, C-reactive protein; ACT, alpha-1 antichymotrypsin; AGP, alpha-1 acid glycoprotein; IL-6, interleukin-6.
B-lymphocytes to immunoglobulin synthesis, the activation and differentiation of T-cells and in the activation of megakaryocytes.

Contradictory data have been produced concerning the role of IL-6 in patients with various malignancies. Antitumor capacities of IL-6 were demonstrated in vitro and in vivo in patients with breast cancer, lung cancer and some leukemia [7-9]. On the other hand, IL-6 supports the growth of myeloma [10]. It has already reported that IL-6 and IL-6-mediated systemic inflammatory response are related to hypermetabolism and cachexia in lung cancer patients [11]. Finally, the elevated serum IL-6 levels are adverse prognostic factor in kidney cancer patients [12].

In the present report, we serially measured the levels of IL-6 and some APP in lung cancer patients undergoing radiotherapy in order to investigate the relationship between the response to the treatment and the changes in parameters of systemic inflammatory response.

MATERIALS AND METHODS

Patients

Sixty-one fully diagnosed patients with early disease (stage 1 or 2) underwent therapy. Patients with evidence of metastases or concomitant acute infection were excluded from the study. The patients were diagnosed based on the radiological picture, bronchoscope and sputum cytology. The clinical diagnosis was confirmed by histopathology (squamous cell carcinoma) in all patients. All patients were resectable but inoperable for medical reasons (i.e., ischemic heart disease or chronic obstructive airway disease) or unresectable. The patients were treated with curative radiotherapy: 200 cGy/T for five consecutive days for six weeks (total dose: 6000cGy/T). Clinical assessments were performed before treatment, and after three, six, nine and 12 months of the treatment. Serum samples were collected at the time clinical assessments were done, and stored in a freezer (-85°C).

Immunological studies

The IL-6 levels were evaluated using a solid-phase sandwich enzyme-linked-immuno-sorbert-assay (ELISA). The kits were supplied by BioSource International (USA). An antibody specific for IL-6 had been coated onto the wells. Samples were pipetted into these wells followed by addition of biotinylated second antibody. During the incubation, the antigen (IL-6) binds simultaneously to the capture antibody on one site, and to the solution phase biotinylated antibody on a second site. After removal of excess second antibody, streptavidin-peroxidase was added. After removing all of the unbound enzyme, a substrate solution was added. The intensity of this colored product was directly proportional to the concentration of the antigen (IL-6) present in the original specimen. The lower limit of detection of IL-6 was 5 pg/ml. C-reactive protein (CRP) serum levels were developed using nephelometry methods. Alpha-1 acid glycoprotein (AGP) and alpha-1 antichymotrypsin (ACT) were measured using rocket immunoelectrophoresis according to Laurell [13]. Microheterogeneity of AGP was employed to differentiate elevation of IL-6 and/or CRP induced by acute infection from induced by cancer [14, 15]. It was performed using crossed affinoimmunoelectrophoresis with concanavalin A as a ligand.

Statistical analysis

The Mann-Whitney rank order test was used to evaluate statistical significance. Relationship between variables was examined using Spearman’s correlation coefficient for continuous variables.
RESULTS

At the inception of the study the detectable levels of IL-6 were found in majority of lung cancer patients (49 cases, 80 percent). Table 2 shows the findings of IL-6 serum level for individual patients. We did not measure the levels of IL-6 and APP immediately after radiotherapy, because we expected their nonspecific elevation connected with postradiation tissues damage. After three, six nine and 12 months detectable levels were observed in 39 of 41 (95 percent), 34 of 39 (87 percent), 29 of 34 (85 percent) and 39 of 52 (79 percent) patients respectively. Originally elevated values of IL-6 decreased during the observation, however, and we did not find these changes to be statistically significant.

CRP serum levels for individual patient are shown in Table 3. The levels of CRP, AGP and ACT were found to be elevated as compared to the control group (Table 1). Twelve months after the curative radiotherapy we did not notice any statistically significant changes in the serum level of APP. However, we established a correlation between IL-6 and CRP at the beginning of the study (r = .638, p < .01) and after 12 months observation (r = .695, p < .01).

For further analysis we divided our patients into two groups depending on the response to the treatment. The first group (referred to as responders) comprised 32 patients with stable disease, partial remission or total remission. Twenty-nine patients with progression of the disease were included to the second group (referred to as non-responders). The second group included six patients who died due to metastases of the cancer during the study. The analysis of the new data showed a decrease in IL-6 serum level (Figure 1) and CRP level (Figure 2) in responders but not in non-responders. Retrospective analysis of the data obtained from the patients who died due to lung cancer showed a consequent augmentation of IL-6 and CRP before the patients’ death (Figure 3).

DISCUSSION

Lung cancer is a widespread malignant neoplasm among men [16]. Although in women the incidences of the breast, large bowel and skin cancers are higher, the fatality rate due to lung cancer is increasing in women, too [16]. Despite progress in recent diagnosis and treatment of lung cancer, the death rate remains high. The prognosis for lung

| Healthy controls: |  |  |  |
|------------------|-----------------|-----------------|-----------------|
| IL-6 (pg/ml)     | CRP (mg/l)      | AGP (mg/l)      | ACT (mg/l)      |
| 9 (<5-17)        | 5 (<2-11)       | 0.5 (0.2-0.8)   | 0.4 (0.1-0.6)   |

Lung cancer pts:

| Before treatment |  |  |  |
|------------------|-----------------|-----------------|-----------------|
| IL-6 (pg/ml)     | CRP (mg/l)      | AGP (mg/l)      | ACT (mg/l)      |
| 46 (<5-231)      | 32 (2-102)      | 1.2 (0.5-3.9)   | 0.7 (0.2-2.0)   |
| 43 (<5-129)      | 36 (5-99)       | 1.3 (0.5-4.8)   | 0.9 (0.3-2.4)   |
| 43 (<5-145)      | 39 (3-112)      | 1.0 (0.4-3.1)   | 0.6 (0.2-1.7)   |
| 41 (<5-216)      | 34 (3-95)       | 0.9 (0.4-3.0)   | 0.7 (0.2-2.3)   |
| 33 (<5-154)      | 27 (<2-84)      | 1.2 (0.4-3.4)   | 0.7 (0.2-1.9)   |

p < .05 (vs. before treatment)
### Table 2. Serum interleukin-6 levels in individual lung cancer patients.

| Patient | Sex | At the onset of study | After 3 mo | After 6 mo | After 9 mo | After 12 mo |
|---------|-----|------------------------|------------|------------|------------|------------|
| **Responders** | | | | | | |
| ec      | m   | <5                     | <5         | <5         | <5         | <5         |
| ks      | m   | <5                     | 26         | 19         |            |            |
| kjl     | m   | <5                     | 23         | 11         |            |            |
| tm      | m   | <5                     | 23         | 11         |            |            |
| hm      | m   | <5                     | 23         | 12         | 10         | <5         |
| cs      | m   | <5                     | 7          | <5         | <5         | <5         |
| kg      | m   | <5                     | 35         | <5         | 9          | 11         |
| nm      | m   | <5                     | 6          | 8          |            |            |
| rl      | m   | <5                     | 7          | 10         |            |            |
| fs      | m   | <5                     | 15         | 44         | <5         |            |
| sb1     | m   | <5                     | 9          | 25         | 29         | <5         |
| mb      | m   | 11                     | 12         | 10         | 6          | <5         |
| ew      | m   | 13                     | 26         | 30         | 85         | <5         |
| tr      | m   | 18                     | 22         | 31         | 14         |            |
| bz      | f   | 19                     | 19         | 25         | 32         |            |
| wf      | m   | 30                     | 37         | 50         | 30         |            |
| bh      | m   | 50                     | 47         | 32         | 14         |            |
| tl      | m   | 51                     | 47         | 32         | 14         |            |
| fb      | m   | 56                     | 67         | 50         | 30         |            |
| ls      | m   | 56                     | 47         | 32         | 14         |            |
| sk1     | m   | 50                     | 53         | 43         | 19         | 55         |
| aj      | m   | 51                     | 19         | 17         |            |            |
| fh      | m   | 56                     | 37         | 32         |            |            |
| sh      | m   | 56                     | 67         | 50         | 30         |            |
| wz      | m   | 56                     | 47         | 32         | 14         |            |
| ts      | f   | 50                     | 66         | 42         | 22         |            |
| ln      | m   | 68                     | 54         | 45         | 34         |            |
| wc      | m   | 69                     | 30         | 30         | 33         |            |
| wb      | m   | 89                     | 68         | 41         |            |            |
| jj1     | m   | 122                    | 87         | 72         | 55         | 78         |
| im      | m   | 203                    | 47         |            |            |            |
| **Non-responders** | | | | | | |
| mw      | m   | <5                     |            |            |            | <5         |
| hp      | m   | <5                     |            |            |            | <5         |
| jm      | m   | 17                     | 11         | 25         | 28         |            |
| tg      | m   | 23                     | 15         | 36         | 31         |            |
| bd      | m   | 26                     | 15         | 26         | 31         |            |
| sk2     | m   | 16                     | 16         | 26         | 31         |            |
| lg      | m   | 110                    | 86         | 37         | 30         |            |
| kj2     | m   | 29                     | 46         | 30         |            |            |
| bw1     | f   | 14                     | 24         | 34         | 35         |            |
| jj2     | m   | 84                     | 74         | 43         | 36         |            |
| ws      | m   | 18                     | 18         | 31         | 38         |            |
| sm      | m   | 28                     | 26         | 31         | 38         |            |
| ar      | m   | 43                     | 35         | 48         |            |            |
| wa      | m   | 20                     | 20         | 54         | 57         |            |
| wp1     | m   | 32                     | 26         | 33         | 40         | 59         |
| jz      | m   | 65                     | 57         | 62         |            |            |
| as      | m   | 79                     | 44         | 66         |            |            |
| sb2     | m   | 58                     | 43         |            |            |            |
| wp2     | m   | 163                    | 145        | 82         | 111        |            |
| mg      | f   | 133                    | 129        | 129        |            |            |
| hb      | f   | 8                      | 8          | 216        | D          |            |
| hk      | m   | 8                      | 8          | 216        | D          |            |
| ap      | m   | 73                     | 89         | 157        | D          |            |
| ep      | m   | 53                     | 48         | 115        | D          |            |
| hw      | m   | 8                      | 8          | 118        | D          |            |
| gb      | f   | 112                    | 64         | 123        | D          |            |
| zp      | m   | 20                     | 57         |            |            |            |
| bs      | f   | 31                     | 27         | 34         | 30         |            |
| bw2     | m   | 45                     | 89         |            |            | D          |
Table 3. Serum C-reactive protein levels in individual lung cancer patients.

| Patient | Sex | At the onset of study | After 3 mo | After 6 mo | After 9 mo | After 12 mo |
|---------|-----|-----------------------|-----------|-----------|-----------|------------|
| Responders                                      |         |                       |           |           |           |            |
| ed      | m   | 4                     | 6         | 7         | 3         | 2          |
| kg      | m   | 7                     | 6         | 40        | 26        |            |
| tm      | m   | 11                    |           | 15        | 13        |            |
| hm      | m   | 43                    | 35        | 26        | 24        | 3          |
| cs      | m   | 4                     | 12        | 12        | 19        | 9          |
| kg      | m   | 5                     | 6         | 3         | 4         | 12         |
| nm      | m   | 4                     | 86        | 29        | 24        | 23         |
| rl      | m   | 25                    |           | 55        |           |            |
| fs      | m   | 14                    |           |           | 39        | 33         |
| sbl     | m   | 17                    | 7         | 26        |           | 17         |
| mb      | m   | 7                     |           | 39        | 10        | 3          |
| ew      | m   | 14                    | 23        | 19        | 9         | 3          |
| tr      | f   | 45                    |           |           |           | 11         |
| wz      | f   | 33                    | 57        |           |           | 26         |
| bh      | m   | 14                    |           |           | 45        |            |
| tl      | m   | 74                    |           |           |           | 16         |
| fb      | m   | 16                    | 99        | 76        |           | 24         |
| ls      | m   | 46                    | 28        | 10        |           | 30         |
| sk1     | m   | 10                    | 7         | 8         | 10        |            |
| aj      | m   | 32                    | 80        | 21        | 41        |            |
| wh      | m   | 43                    | 5         |           |           |            |
| sh      | m   | 18                    | 5         | 25        | 7         |            |
| wz      | m   | 65                    |           |           | 7         | 6          |
| la      | m   | 27                    | 30        | 31        | 29        | 18         |
| ts      | m   | 56                    | 48        | 42        | 23        | 21         |
| ln      | m   | 3                     | 12        | 4         | 3         | 2          |
| wc      | m   | 39                    | 58        | 42        | 22        | 15         |
| wb      | m   | 34                    | 9         | 31        | 19        |            |
| jj1     | m   | 61                    | 43        | 67        | 49        | 48         |
| im      | m   | 75                    |           |           |           | 35         |
| Non-responders                                  |         |                       |           |           |           |            |
| mw      | m   | 37                    |           |           |           | 47         |
| hp      | m   | 15                    |           |           |           | 34         |
| jm      | m   | 45                    | 6         | 23        | 39        | 26         |
| tg      | m   | 49                    |           |           |           | 37         |
| bd      | m   | 29                    | 47        | 70        | 62        | 35         |
| sk2     | m   | 5                     | 12        | 26        | 68        | 31         |
| ig      | m   | 57                    | 48        | 20        | 31        | 22         |
| kj2     | m   | 30                    | 27        | 68        |           | 23         |
| lw      | f   | 12                    | 35        | 29        | 51        | 46         |
| jj2     | m   | 38                    | 24        | 11        | 15        | 9          |
| ws      | m   | 21                    | 23        | 31        | 40        | 38         |
| sm      | m   | 39                    | 16        |           |           | 47         |
| ar      | m   | 9                     | 52        |           |           | 43         |
| wa      | m   | 34                    |           |           | 16        | 52         |
| wpl     | m   | 35                    | 36        | 42        | 34        | 42         |
| jz      | m   | 18                    |           | 58        |           | 19         |
| as      | m   | 42                    |           |           | 57        | 26         |
| sb2     | m   | 37                    | 64        |           |           | 84         |
| wp2     | m   | 72                    |           |           |           | 44         |
| mg      | m   | 102                   | 82        | 112       | 73        | 66         |
| hb      | f   | 47                    |           |           |           | 82         |
| hk      | m   | 28                    | 38        | 57        | 95        | D          |
| ap      | m   | 43                    | 44        | 56        | 78        | D          |
| ep      | m   | 19                    | 56        | 84        |           | D          |
| hw      | m   | 9                     | 45        | 67        |           | D          |
| gb      | f   | 42                    | 60        | 69        |           | D          |
| zp      | m   | 41                    | 69        |           |           |            |
| bs      | f   | 52                    | 24        | 40        | 48        | 35         |
| bw2     | m   | 19                    | 45        |           |           | D          |

m- male, f - female, D - died
A.

Figure 1. The changes in IL-6 serum levels in lung cancer patients undergoing radiotherapy. A: Responders; B: Non-responders.
Figure 2. The changes in CRP serum levels in lung cancer patients undergoing radiotherapy. A: Responders; B: Non-responders.
cancer is best if it is detected in presymptomatic stage, and the treatment is more effective if we can easily control the changes in the disease progression. Therefore, we are looking for prognostic markers for better diagnosing and monitoring patients suffering from lung cancer.

A number of different laboratory parameters and indices have been already employed to detect lung cancer progression/remission score. However, none is widely used or has found universal acceptance as a standard. A group of acute-phase proteins seemed to be

Figure 3. The changes in IL-6 and CRP in 6 lung cancer patients who died during the study.
very promising [17-19]. The evaluation is simple, fast and cheap, but it is very nonspecific and any infection may produce positive findings. Therefore, cytokines controlling acute-phase response (APR) became a subject of investigation. IL-6 the main APR activator has been the most interesting [11, 20].

In the present study we serially evaluated the serum level of IL-6, CRP, AG and ACT. IL-6 has been found strongly elevated in lung cancer patients and these data are in accordance with the results of others [11, 20, 21]. Moreover, the levels of APP were also significantly elevated. However, the most interesting results were obtained after retrospective analysis of the data of six patients who died during the study period. The levels of IL-6 and CRP increased progressively before the death.

Following the changes in acute-phase response and interleukin-6 serum levels in lung cancer patients, seems to be helpful in prognosis of the disease. Based on these data, we suggest that an elevation in IL-6 and/or CRP level in patients with lung cancer may serve as an adverse prognostic factor. However, it will need further investigation.

REFERENCES

1. Akira, S. and Kishimoto, T. IL-6 and NF-IL-6 in acute-phase response and viral infection. Immunol. Rev. 127:25-48, 1992.
2. Defrance, T., Vanbervliet, B., Briere, F., Durand, I., Rousset, F., and Banchereau, J. Interleukin-10 and transforming growth factor beta cooperate to induce anti CD40 activated naive human B cells to secrete immunglobulin A. J. Exp. Med. 175:671-682, 1992.
3. Richards, C.D., Brown, T.J., Shoyab, M., Baumann, H., and Gauldie, J. Recombinant oncostatin M stimulates the production of acute-phase proteins in HepG2 cells and rat primary hepatocytes in vitro. J. Immunol. 148:1731-1736, 1992.
4. Schoolink, H., Stoyan, T., Roeb, E., Heinrich, P.C. and Rose-John, S. Ciliary neutrophic factor induces acute-phase protein expression in hepatocytes. FEBS Lett. 314:280-284, 1992.
5. Gauldie, J., Richards, C., Harnish, D., Landsdorp, P. and Baumann, H. Interferon beta-2/B-cell stimulatory factor type 2 shares identity with monococyte-derived hepatocyte-stimulating factor and regulates the major acute-phase response in liver cells. Proc. Natl. Acad. Sci. USA 84:7251-7255, 1987.
6. Le, J. and Vilecek, J. Biology of disease. Interleukin-6: A multifunctional cytokine regulating immune reactions and the acute-phase proteins response. Lab. Inv. 61:588-595, 1989.
7. Givon, T., Slavin, S., Haran-Ghera, N., Michalevicz, R. and Revel, M. Antitumor effects of human recombinant interleukin-6 on acute myeloid leukemia in mice and in cell cultures. Blood 79:2392-2398, 1992.
8. van Gameren, M.M., Willemsen, P.H.B., Mulder, N.H., Limburg, P.C., Groen, H.J.M., Vellenga, E. and de Vries, E.G.E. Effects of recombinant human interleukin-6 in cancer patients: a phase I-II study. Blood 84:1434-1441, 1994.
9. Veldhuis, G.J., Willemsen, P.H.B., Sleijfer, D.T., van der Graaf, W.T.A., Groen, H.J.M., Limburg, P.C., Mulder, N.H. and de Vries, E.G.E. Toxicity and efficacy of escalating dosages of recombinant human interleukin-6 after chemotherapy in patients with breast cancer or non-small-cell lung cancer. J. Clin. Oncol. 13:2585-2592, 1995.
10. Zhang, X.G., Klein, B. and Bataille, R. Interleukin-6 is a potent myeloma-cell growth factor in patients with aggressive multiple myeloma. Blood 74:11-13, 1989.
11. Staal-van den Brekel, A.J., Deten, M.A., Schols, A.M.W.J., Buurman, W.A. and Wouters, E.F.M. Increased resting energy expenditure and weight loss are related to a systemic inflammatory response in lung cancer patients. J. Clin. Oncol. 13:2600-2605, 1995.
12. Blay, J.Y., Negrier, S., Combaret, V., Attali, S., Goillot, E., Merrouche, Y., Mercatello, A., Ravault, A., Tourani, J.M. and Moskovtchenko, J.F. Serum level of interleukin-6 as a prognostic factor in metastatic renal cell carcinoma. Cancer Res. 52:3317-3322, 1992.
13. Laurell, C.B. Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. Scand. J. Clin. Invest. 12(4Suppl.):2-28, 1973.
14. Fassbender, K., Zimmerli, W., Kissling, R., Sobieska, M., Aeschlimann, A., Kellner, M. and Muller, W. Glycosylation of alpha 1-acid glycoprotein in relation to duration of disease in acute and chronic infection and inflammation. Clin. Chim. Acta 203:315-327, 1991.
15. Mackiewicz, A., Marcinkowska-Pieta, R., Ballou, S., Mackiewicz, S. and Kushner, I. Microheterogeneity of alpha-1-acid glycoprotein in the detection of intermittent infection in systemic lupus erythematosus. Arthritis Rheum. 30:513-517, 1987.
16. Spiro, S.G. Epidemiology of lung cancer. In: Hoogstraten, B., Addis, B.J., Hansen, H.H., Martini, N. and Spiro, S.G. (eds.). Lung Tumors: Berlin-Heidelberg-New York-London-Paris-Tokyo: Springer-Verlag; 1991, pp. 3-8.
17. Hansen, J.E., Iversen, J., Lihme, A. and Bog-Hansen, T.C. Acute-phase reaction, heterogeneity and microheterogeneity of serum proteins as nonspecific marker in lung cancer. Cancer 60:1630-1635, 1987.
18. Milroy, R., Shapiro, D., Shenkin, A., and Banham, S.W. Acute-phase reaction during chemotherapy in small cell lung cancer. Br. J. Cancer 59:933-935, 1989.
19. Tamura, S., Nishigaki, T., Moriwaki, Y., Fujioka, H., Nakano, T., Fujii, J., Yamamoto, T., Nabeshima, K., Hada, T. and Higashino, K. Tumor markers in pleural effusion diagnosis. Cancer 61:298-302, 1988.
20. Yanagawa, H., Sone, S., Takahashi, Y., Haku, T., Yano, S., Shinohara, T., and Ogura, T. Serum level of interleukin-6 in patients with lung cancer. Br. J. Cancer 71:1095-1098, 1995.
21. Wojciechowska-Lacka, A., Matecka-Nowak, M., Adamiak, E., Lacki, J.K., and Cerkaska-Gluszak, B. Serum levels of interleukin-10 and interleukin-6 in patients with lung cancer. Neoplasma 43:155-158, 1996.