Serum levels of interleukin-18 (IL-18) and soluble interleukin-2 Receptor (sIL-2R) in lung cancer

Naumnik W[1], Chyczewska E[1], Kovalchuk O[2], Tałałaj J[1], Iżycki T[1], Panek B[1]

[1] Department of Pneumonology and Tuberculosis; Medical University of Bialystok, Poland
[2] Department of Clinical Molecular Biology, Medical University of Bialystok, Poland

Abstract

Purpose: We evaluated the clinical usefulness of interleukin-18 (IL-18) and soluble interleukin-2 receptor (sIL-2R) during chemotherapy of lung cancer in relation to the histological type of the tumor, clinical stage, response to therapy and time survival.

Material and methods: Serum levels of IL-18 and sIL-2R were determined in 73 patients (62 males; mean age 64 years; 41 with non-small cell lung cancer-NSCLC, 32 with small cell lung cancer-SCLC); 12 healthy subjects served as controls. To determine IL-18 serum concentrations (Elisa), venous blood samples were collected from each patient before and after chemotherapy.

Results: The mean serum IL-18 level in all patients with lung cancer was significantly higher compared with healthy volunteers ($p=0.0001$; NSCLC vs control $p=0.0001$; SCLC vs control $p=0.004$). In NSCLC group with stage IV the mean IL-18 level was significantly higher than those with stage IIIB ($p=0.04$). Regardly to tumor stage as well as in relation to response to therapy, no significant differences in IL-18 were observed. Using cut-off serum IL-18 concentration of 319.6 pg/ml, the prognoses of the two groups were different, but it was not statistically significant. The serum levels of sIL-2R in NSCLC patients were significantly higher than in controls ($p=0.018$). There were no significant differences in serum sIL-2R levels in relation to clinical stage of lung cancer and response to therapy. The cut-off value between high and low serum sIL-2R concentration was defined as 582.27 U/ml. The difference in survival rate between the high and low sIL-2R groups was not significant.

Conclusions: Serum IL-18 and sIL-2R levels can be useful in clinical practice, but their practical significance needs further studies.

Keywords: interleukin-18 (IL-18), soluble interleukin-2 receptor (sIL-2R), small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), chemotherapy.

Introduction

Interleukin 18 (IL-18) is a novel immunoregulatory cytokine that was known previously as interferon-gamma-inducing factor (IFN-γ) [1]. This cytokine is produced by activated macrophages, keratinocytes, Kupffer cells, intestinal epithelial cells, and osteoblasts [1]. The high levels of IL-18 have been detected in cancer patients (hematologic malignancies, gastric carcinoma, breast carcinoma) [2,3,4]. There are not data about IL-18 in lung cancer. IL-18 enhance the development of T-helper cells (Th1) that seems to play a crucial role in the generation of antitumor immunity [5]. IL-18 induces the production of IL-2 from Th1 cells [6]. The combined use (in vitro) of these two cytokines synergistically enhance the proliferation, cytolytic activity, and interferon-gamma production of peripheral blood mononuclear cells [7]. The activated mononuclear cells can release a soluble form of interleukin 2 receptors (sIL-2R) in the blood. Serum sIL-2R level is a sensitive and quantitative marker of circulating peripheral blood mononuclear cell activation [8]. This molecule acts as an antagonist of IL-2-mediates responses [9]. sIL-2R levels reflect T-cell activation and correlate with the disease activity [10,11]. To determine the clinical importance of IL-18 in lung cancer patients in the current study, we measured serum IL-18 and sIL-2R levels. We were curious about the correlation

ADDRESS FOR CORRESPONDENCE:
Wojciech Naumnik
Department of Pneumonology and Tuberculosis
Medical University of Bialystok
ul. Żurawia 14
15-540 Bialystok, Poland
Tel/Fax: +48 85 732 41 49
e-mail: naumw@mp.pl

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between IL-18 and sIL-2R serum levels. We analyzed the levels of IL-18 and sIL-2R in lung cancer in relation to the histological type of the tumor, clinical stage, response to therapy and time survival for patients.

Materials and methods

Patients

The study included 73 patients with carcinoma of the lung, who where admitted to the Department of Pneumonology, Medical Academy in Bialystok from 1999 to 2002. They consisted of 62 males and 11 females (mean age of 64.0 years; ranged 29-78). The tumors were histologically classified as adenocarcinoma in 8 cases, squamous cell carcinoma in 33, and small cell carcinoma in 32. None of the patients suffered from infectious, allergic, autoimmune, or other systemic diseases such as diabetes mellitus and hypertension. The patients had not been previously treated with chemotherapy. The control group for serum IL-18 concentrations comprised 12 healthy volunteers (10 males) with mean age of 61 years. There were no significant differences in age and sex between patients and controls. All patients had a history of smoking.

Methods

Before receiving treatment, patients underwent standard staging procedures consisting of physical examination, serum chemistry examination, bronchoscopy, chest CT scan and ultrasonography of abdomen. Further imaging techniques were used when required clinically. The clinical stage of non small cell lung cancer (NSCLC) was assigned according to the International Union Against Cancer (TNM classification). The classifications of small cell lung cancer (SCLC) were made according to the Veterans Administration Lung Cancer Study Group (LD-limited disease; ED-extensive disease). After staging, the patients were placed on cisplatin or platin-derived chemotherapy, which was coupled with radiotherapy in the locally advanced forms. Standard criteria for objective response to therapy were used (WHO guidelines). To exclude the possible interference of chemotherapy, subsequent blood samples were obtained at least 28 days after the last administration of cytotoxic drugs. To determine IL-18 serum concentrations, venous blood samples were collected from each patient before and after IV cycles chemotherapy (some of the patients underwent later radiotherapy). Serum samples were obtained by centrifugation and stored at -80°C until assayed. Serum IL-18 concentrations were measured by a single labolatory with an enzyme immunoassay (Human IL-18 ELISA Kit; MBL, Japan; sensivity: < 12.5 pg/ml) according to the manufacturer's instructions. The sera were assayed for sIL-2R with an enzyme – linked immunosorbent assay using Cellfree Human Elisa sIL-2R Kits (Endogen, USA; sensivity: < 24 U/ml). All samples were assayed in duplicate.

Statistical analysis

Data were presented as mean ± 1 SD or median (range), depending on their normal or skewed distribution provided by Shapiro-Wilk's W test. Data for IL-18 and sIL-2R concentrations in serum samples from healthy subjects and from patients with lung cancer were analyzed using Student's T-test for independent samples. Differences among groups of patients before and after chemotherapy were determined using Student's T-test for dependent samples. In the case of skeweew distribution the data were analysed using Wilcoxon's-test and Mann-Whitney's U-test for unpaired data. Correlation between the parametres were calculated by the Spearman's and Pearson's rank tests.

Survival curves were generated using the Kaplan-Meier's method, and the significance of the difference in survival rates was determined by the log-rank test. Multivariate analysis was performed using a Cox's proportional hazards model. All patients with lung cancer were divided into two groups according to their IL-18 and sIL-2R serum levels. The cut-off point was set at 319.6 pg/ml for IL-18 and 582.27 U/ml for sIL-2R. The cut-off points represented the mean ± 1 SD of serum IL-18 and sIL-2R values in healthy volunteers.

All p values were two-tailed, and values less than 0.05 were considered statistically significant. Computations were performed using Statistica 6.0 for Windows (StatSoft Inc., Tulsa, Okla, USA).

Results

Serum IL-18 and sIL-2R levels in healthy volunteers and patients with lung cancer

As shown in *Tab. 1*, the serum IL-18 levels in 73 patients with lung cancer were significantly higher compared with the 12 healthy volunteers ($p = 0.0001$; NSCLC vs control $p = 0.0001$; SCLC vs control $p = 0.004$). There were no significant differences in serum IL-18 levels with regard to patient age or gender, or histologic type.

The serum sIL-2R levels in lung cancer patients were significantly higher than in control ($p = 0.023$; NSCLC vs control $p = 0.018$) (*Tab. 1*). The difference between patients with NSCLC and SCLC was not significant and the levels of sIL-2R in SCLC did no differ significantly from control group.

There was a positive correlation between IL-18 and sIL-2R in NSCLC group ($p = 0.020$; $r = 0.360$).

Serum IL-18 and sIL-2R levels in relation to clinical stage of the tumor

In NSCLC group (*Tab. 1*) the mean IL-18 level of patients with stage IV was significantly higher than those with stage IIIB ($p = 0.04$). No significant differences in serum IL-18 levels with regard to tumor stage of SCLC were observed (*Tab. 1*).

There were no significant differences in serum sIL-2R levels in relation to clinical stage of NSCLC and SCLC (*Tab. 1*).

Serum IL-18 and sIL-2R levels in relation to response to therapy

There were no significant differences in serum IL-18 levels in relation to response to therapy (*Tab. 2*). No significant differences in serum sIL-2R levels with regard to response to therapy were observed (*Tab. 2*).

Table 1. **Serum IL-18 and sIL-2R levels in lung cancer patients and controls**

Disease stage		before chemotherapy (p-VALUE VS CONTROLS)	after chemotherapy (p-VALUE VS CONTROLS)	Controls (n = 12)
Lung carcinoma patients (n = 73)	IL-18 sIL-2R	390.9 ± 151 p = 0.0001 602.3 (65 - 2016) p = 0.023	498.2 ± 314 p = 0.00006 840.8 (41 - 7233) p = 0.014	227.3 ± 92 516.7 (281 - 596)
NSCLC (n = 41)	IL-18 sIL-2R	411.0 ± 144 p = 0.0001 625.6 (65 - 2016) p = 0.018	494.5 ± 316 p = 0.00004 614.7 (41 - 4431) p = 0.012	
III A (n = 4)	IL-18 sIL-2R	341.3 ± 80 613.9 (471 - 640)	524.7 ± 150 992.9 (640 - 1419)	
III B (n = 12)	IL-18 sIL-2R	338.8 ± 118 # 574.7 (65 - 5016)	384.9 ± 114 509.4 (41 - 1568) *	
IV (n = 25)	IL-18 sIL-2R	442.8 ± 144 ## 696.1 (153 - 1932)	475.1 ± 209 614.7 (330 - 2060)**	
SCLC (n = 32)	IL-18 sIL-2R	370.9 ± 157 p = 0.004 567.5 (137 - 1889)	506.1 ± 309 p = 0.005 589.3 (169 - 7233)	
LD (n = 13)	IL-18 sIL-2R	435.4 ± 189 567.5 (313 - 978)	526.8 ± 249 560.9 (169 - 959)	
ED (n = 19)	IL-18 sIL-2R	326.9 ± 116 562.3 (137 - 1889)	489.1 ± 209 603.4 (265 - 7233)	

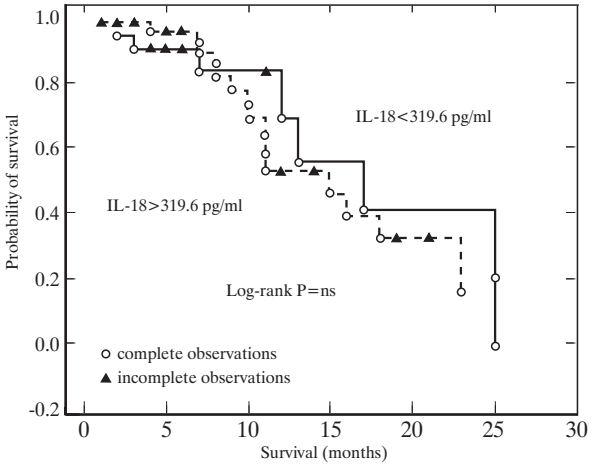
Abbreviations: IL-18 – interleukin 18 (pg/ml); sIL-2R – soluble interleukin 2 Receptor (pg/ml); # vs ## p = 0.04 ; * vs ** p = 0.04

Table 2. **Values of IL-18 and sIL-2R before and after chemotherapy of lung cancer patients**

NSCLC (n = 41)	**PR (n = 14)**		**NC (n = 16)**		**PD (n = 11)**	
	before chemotherapy	after chemotherapy	before chemotherapy	after chemotherapy	before chemotherapy	after chemotherapy
IL-18 sIL-2R	386.2 (230 – 537) 613.9 (257 - 946)	447.4 (184 - 977) 550.4 (137 - 1419)	407.9 (171 – 607) 523.9 (65 - 1315)	390.6 (269 - 1091) 603.8 (41 - 2060)	349.3 (135 – 652) 858.6 (129 - 2016)	380.9 (154 -718) 698.2 (241 - 1568)
SCLC (n = 32)	**PR (n = 17)**		**NC (n = 4)**		**PD (n = 11)**	
	before chemotherapy	after chemotherapy	before chemotherapy	after chemotherapy	before chemotherapy	after chemotherapy
IL-18 sIL-2R	334.8 (146 - 942) 525.6 (137 - 1889)	414.1 (163 – 1265) 582.0 (265 - 7233)	363.5 (234 - 521) 978.8 (654 - 1195)	616.9 (287 - 1109) 690.9 (554 - 1050)	381.1 (195 - 652) 567.5 (426 - 727)	453.5 (164 - 1336) 509.4 (169 - 810)

PR – partial response; NC – no change; PD – progressive disease

Figure 1. **Probability of survival for lung cancer patients in relation to their serum IL-18 levels**



Serum IL-18 and sIL-2R levels in relation to time survival for patients

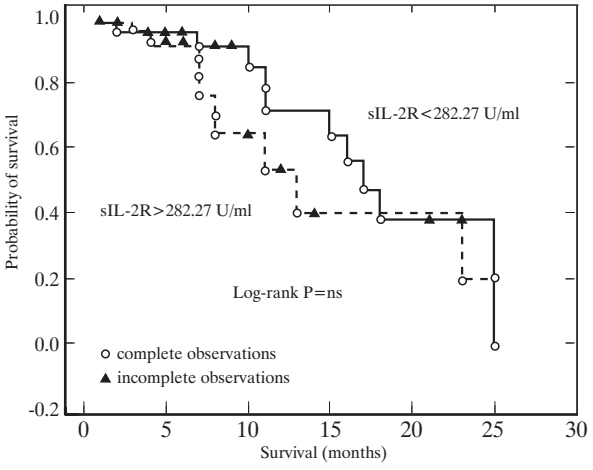
When all patients with lung cancer were divided into high and low groups using cut-off serum IL-18 concentration of 319.6 pg/ml, the prognoses of the two groups were different, but it was not statistically significant (*Fig. 1*).

The cut-off value between the high and low serum sIL-2R concentration was defined as 582.27 U/ml. There was no statistical difference in survival rate between the high and low sIL-2R groups (*Fig. 2*).

Discussion

IL-18 enhanced the immune defense against tumor cells by activating and inducing the production of IFN-γ [12]. In addition to its IFN-γ- enhancing capacity, IL-18 also augments the cytotoxic activity of natural killer (NK) and T-cells and enhances

***Figure 2*. Probability of survival for lung cancer patients in relation to their serum sIL-2R levels**



their production of other proinflammatory mediators such as TNF-α, IL-1β, IL-8 [13,14]. IL-18 elicits antitumor immunity in the murine system by inhibiting tumor angiogenesis, reducing tumorigenesis, and inducing apoptosis in tumor cells [12,13,15, 16]. Although elevated serum IL-18 levels have been reported in patients with renal cancer [17], esophageal cancer [18], breast cancer [4], hematologic malignancies [19], the clinical impact of IL-18 remains unclear in patients with solid tumors. To our knowledge, the current study is the second to report serum IL-18 levels in patients with lung cancer. The first was Lissoni at al., who observed no significant differences in IL-18 mean levels between non-metastatic patients and controls [20]. The patients with metastases of lung cancer had higher IL-18 levels than controls [20]. The same observations were made by Lissoni in patients with gastrointestinal tumors [20].

Our study showed that all patients with lung cancer had higher IL-18 serum levels than healthy volunteers. There were NSCLC patients with stage IIIA, IIIB, and IV in our study. The mean serum IL-18 level of patients with stage IV (i.e. the metastatic patients) was significantly higher compared with patients who had stage IIIB.

Our results are in agreement with increased IL-18 levels evidenced in patients with advanced neoplasma disease as shown by Gunel and Merendino separately [4,21]. They showed that serum IL-18 levels were higher in the metastatic patients compared with the nonmetastatic ones. They measured serum IL-18 levels in breast carcinoma patients. In Merendino opinion IL-18 could act as a marker for metastatic breast cancer [21].

We did not observed significant differences in serum IL-18 levels with regard to tumor size and lymph node metastases. The same observations were made by Kawabata and coworkes in patients with gastric carcinoma [3].

In our study there were no statistical differences in SCLC group between stage ED and LD. These observations confirm that different mechanisms are responsible for IL-18 increase in solid tumors. IL-18 is produced mainly by macrophages, but it is not clear which cells synthesize IL-18 in different circumstances and which conditions favor IL-18 production. IL-18 production may be induced in response to tumor cells or other factors related to tumor growth [3,4]. The high serum IL-18 levels in lung cancer patients may reflect the degree of defense mechanisms against tumor growth and metastasis.

In our studies, there were no significant differences in respect to response to therapy. To our knowledge, the current study is the first to report serum IL-18 in relation to response to therapy of the lung cancer. Kawabata et al. in gastric carcinoma patients showed that serum IL-18 level after surgical resection was significantly lower than before surgery [3]. The mean serum IL-18 level after surgery was similar to that of the controls [3]. These observations suggested that measuring of IL-18 can be useful in monitoring treatment of tumors. However, the clinical impact of IL-18 remains unclear in lung cancer patients who underwent chemotherapy.

It has been reported that elevated serum IL-18 levels also were observed in patients with gastric carcinoma, colorectal carcinoma, non-hodgkin's lymphoma and was associated with a poor prognosis [2,3,22]. Akahiro et al. [23] showed that IL-18 serum levels were correlated with overall survival, although they were shown not to be an independent prognostic factor. In our study, although it was without statistical significance, the patients with lung cancer in each stage who had high serum IL-18 levels also experienced poorer survival compared with patients who had low serum IL-18 levels.

IL-18 synergizes with IL-2 to enhance cytotoxity, IFN-γ production, and expansion of NK cells [7]. Activation of T lymphocytes leads to the expression of interleukin 2 receptor on the cell surface as well as the release of soluble IL-2R molecules into the circulation [11]. T lymphocytes are the predominant IL-2R bearing cells and hence serum sIL-2R level provides a satisfactory indicator of T-cell activation in vivo [10,11]. A soluble form of the IL-2 receptor, consisting of an incomplete variety of alpha chain, retains the ability to bind IL-2 [24]. The high levels of sIL-2R shown in many instances where IL-2-dependent functions are coincidentally impaired, suggest that the molecule may act as an antagonist of IL-2-mediated cell response. Abnormally high levels of sIL-2R have been described in both hemolymphopoietic tumors and solid tumors [25,26]. A lot of studies have revealed increased sIL-2R levels in lung cancer [9,11,27,28]. sIL-2R levels reflect T-cell activation and correlate with the disease activity [10,11].

Our studies showed that we observed a correlation between IL-18 and sIL-2R levels in NSCLC group. Our results are in agreement with observations made by Son et al. [7]. They showed that combined use of IL-18 and IL-2 substantially enhanced the cytolytic activity of peripheral blood mononuclear cells [7].

The behaviour of serum sIL-2R levels in lung cancer patients is controversy.

In our studies serum levels of sIL-2R were significantly higher in cancer patients than in controls. We did not observe significant differences in respect to clinical stage of NSCLC according to TNM classification. Our results are in agreement with studies showed by Orditura et al. [25].

It has been reported that the measuring of sIL-2R can be useful in monitoring chemotherapeutic treatment [9,25]. A reduction in sIL-2R serum levels is generally associated with

a full or partial response to chemotherapy, while they increase during a progression of the disease in spite of the treatment [10]. Conversely, we did not observe significant differences in serum sIL-2R levels with regard to response to chemotherapy.

In some clinical studies, serum concentration of sIL-2R may be a prognostic factor in patients with lung cancer [9,21]. Tisi et al. showed, that the evaluation of sIL-2R serum levels in the postoperative period may have prognostic importance in predicting the risk of early relapse in patients with operable NSCLC [29]. The evidence of a significant association between sIL-2R increases in the postoperative period and early recurrence rate suggested that host immune factors played at least some role in the prognosis of lung neoplastic disease [29]. It has been reported that the patients with abnormal levels of sIL-2R had a worse prognosis, and this could be useful in prognostication [30]. In our study, although it was without statistical significance, the patients with lung cancer in each stage who had high serum sIL-2R levels also experienced poorer survival compared with patients who had low serum sIL-2R levels.

According to our data there were no significant differences in serum sIL-2R levels with regard to histological type of the tumor. The same observations were made by Buccheri, Brunetti and Sarandakou separately [11,10,27]. They noticed a higher sIL-2R concentration in the serum of SCLC patients as compared to that of NSCLC patients, whereas Yano et al. came to opposite conclusions [28]. Moreover in the case series studies by Lissoni et al. there was no distinction in the group of SCLC patients between limited and extended disease [22]. In our study we have made the same observations like Lissoni et al. [26]. We showed that the levels of sIL-2R in SCLC did not differ significantly from healthy volunteers. In NSCLC patients the levels of sIL-2R were significantly higher than in controls.

These observations confirm that different mechanisms are responsible for sIL-2R increase in solid tumors. The leader hypothesis links the sIL-2R increase in solid tumors to the release from activated cells (lymphocytes, macrophages) to express IL-2R during immune-reactions against cancer spreading [25]. Contrary, the increase of sIL-2R levels could be seen as a consequence of a lymphocyte functional damage in patients with solid tumors. Alternatively, it could contribute to the condition of immuno-depression in solid tumors, by means of the competition with cell surface receptor for IL-2 [25].

Concluding, the measuring of IL-18 and sIL-2R can be useful in clinical practice. The clinical significance in monitoring chemotherapy, prognosis of lung cancer needs further studies.

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