Serum levels of Osteoprotegerin (OPG) and Pro Gastrin Releasing Peptide (ProGRP) during chemotherapy of lung cancer

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Abstract

The aim of our study was to evaluate the usefulness of serum OPG and ProGRP during chemotherapy of lung cancer in relation to the histological type of the tumour, its clinical stage and the response to therapy. The levels of OPG and ProGRP were determined in 39 patients (20 NSCLC, 19 SCLC) and 10 healthy subjects. Blood samples were collected from each patient before and after chemotherapy. OPG and ProGRP levels in all the patients with lung cancer were higher than those in the controls. ProGRP were higher in SCLC group than in those NSCLC. In NSCLC group (after chemotherapy), OPG level in patients with Stage IV tumour was higher than in those with Stage IIIB (p=0,03). OPG in ED SCLC were higher than those in LD SCLC (p=0.04). In SCLC group, ProGRP were higher in LD patients than those with ED (p=0.04). Concluding, the measuring of OPG and ProGRP in lung cancer patients may be useful in clinical practice.

Key words: Osteoprotegerin (OPG), Pro Gastrin Releasing Peptide (ProGRP), lung cancer, non-small cell lung cancer-NSCLC, small cell lung cancer-SCLC.

Introduction

Lung cancer is one of the most prominent causes of mortality - because of neoplastic reasons - in industrialized countries, in particular, among the male population.

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OPG is a novel secreted member of the tumour necrosis factor superfamily [1]. OPG binds RANKL (receptor activator of NF-κB ligand), inhibiting its interaction with RANK and preventing osteoclast formation [2]. It has been reported that OPG expression is associated with bone metastasis of cancer [2]. High levels of OPG mRNA have been detected in the lung, the heart, the kidney, the liver, the stomach, the intestine and bones [1, 3]. It has been reported that the expression of OPG protein in gastric carcinoma tissues correlates with the clinical stage of the tumour [4]. The data about OPG in lung cancer patients are rather poor. Lipton et al. [5] have reported that there is no difference in serum OPG levels between healthy controls and lung cancer patients (16 pts). There were no observations, concerning the clinical stage and the histological type of the tumour.

ProGRP, a member of the bombesin family of peptides, has been shown to be produced by SCLC in an autocrine fashion [6]. It has been suggested that ProGRP is a potential tumour marker for SCLC [6]. In the SCLC chemotherapy group, ProGRP was higher in progressed patients than in the responders [6]. In order to determine the clinical significance of OPG and ProGRP in lung cancer patients, we analyzed levels of these proteins in relation to the histological type of the tumour, its clinical stage and response to therapy.

Materials and methods

The study included 39 patients (smokers; 20 NSCLC; 19 SCLC). The group consisted of 35 males and 4 females (the mean age of 64.0 years; the age range: 29-78 years). At the time of examination, the patients did not show any signs of clinically overt active inflammatory process. The control group comprised 10 healthy volunteers with the mean age of 61 years (non smokers, 8 males). The clinical stage of NSCLC was assigned, according to TNM classification. The classifications of SCLC were made, according to the VALCSG (LD-limited disease; ED-extensive disease). Standard criteria for the objective response to the applied therapy were used (WHO guidelines). Blood samples

Table 1. Serum OPG and ProGRP levels in lung cancer patients and controls.

Disease stage	before chemotherapy (P-VALUE VS CONTROLS)	after chemotherapy (P-VALUE VS CONTROLS)	Controls (n = 10)
patients (n=39) OPG Pro GRP	4,2 ± 1,2 p=0,003 30,8 (9 – 113)	4,2± 1,0 p=0,002 34,3 (13 – 305)	3,1 ± 0,6 21,8 (10 – 33)
NSCLC (n=20) OPG Pro GRP	4,2 ± 1,2 p=0,011 30,8 (9 – 113) p=0,011	4,5 ± 1,2 p=0,001 34,3 (13 – 305) p=0,001	
IIIB (n = 11) OPG Pro GRP	3,8 ± 1,2 25,7 (13 – 43)	3,9 ± 0,9 * 32,9 (17 – 41)	
IV (n = 9) OPG Pro GRP	4,6 ± 1,1 33,6 (9 – 113)	5,2 ± 1,3 ** 37,1 (13 – 305)	
SCLC (n = 19) OPG Pro GRP	4,3 ± 1,1 p=0,005 1152,2 (26–1802) p=0,00002	4,0 ± 0,6 p=0,0008 255,4 (18 – 1581) p=0,0001	
LD (n = 9) OPG Pro GRP	4,2 ± 1,0 1589,9 (39 – 1802)	3,7± 0,5 # 262,8 (63 – 1236) 1	
ED (n =10) OPG Pro GRP	4,5 ± 1,2 925,2 (26 – 1763)	4,3 ± 0,6 # # 67,6 (18 – 1581) 2	

Abbreviations: OPG- osteoprotegerin (pmol/l); Pro GRP - Pro Gastrin Releasing Peptide (pmol/l);
* vs ** p=0,03; # vs # # p=0,04; 1 vs 2 p=0,04

Table 2. Values of OPG and ProGRP before and after chemotherapy of lung cancer patients

	PR + NC (n = 11)		PD (n = 9)	
NSCLC (n = 20)	before chemotherapy	after chemotherapy	before chemotherapy	after chemotherapy
OPG Pro GRP	4,0 ± 1,2 30,8 (13 – 38)	4,2 ± 1,2 35,7 (19 – 74)	4,4 ± 1,3 23,5 (9 – 113)	4,7 ± 1,4 31,5 (13 – 305)
	PR + NC (n = 11)		PD (n = 8)	
SCLC (n = 19)	before chemotherapy	after chemotherapy	before chemotherapy	after chemotherapy
OPG Pro GRP	4,4 ± 1,0 1152,2 (39 – 1802)	4,0 ± 0,7 79,7 (18 – 1236)	4,3 ± 1,3 1375,0 (26 – 1763)	4,0 ± 0,6 1012,8 (48 – 1581)

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

were collected from each patient before and after chemotherapy. Serum OPG and ProGRP concentrations were measured by enzyme immunoassay (Biomedica-OPG; IBL Japan-ProGRP) Statistical differences were analyzed by Student's t test, the non-parametric Wilcoxon test and the Mann- Whitney's U- test. Any value of $p<0,05$ was considered statistically significant.

Results

As shown in Tab. 1, serum OPG and ProGRP levels in 39 patients with lung cancer were higher than those in the controls. No significant differences in serum OPG levels were observed with regard to the histological type of the tumour (Tab. 1). ProGRP were significantly higher in the SCLC group than in NSCLC (Tab. 1). In the NSCLC group (after chemotherapy) (Tab. 1), the mean OPG level in patients with Stage IV was higher than that in patients with Stage IIIB (p=0.03). OPG in ED SCLC were higher than those in LD SCLC (p=0.04). In the SCLC group, ProGRP were higher in LD patients than in those with ED (p=0.04) (Tab. 1). No significant differences in ProGRP levels were observed with regards to the tumour stage of NSCLC (Tab. 1). No differences in OPG and ProGRP levels were observed with regards to the response to applied therapy (Tab. 2).

Discussion

OPG is a key factor, inhibiting the differentiation and activation of osteoclasts, and is, therefore, essential for bone resorp-

tion. In healthy people, osteoclastic activity is regulated by the balance between OPG and its ligand (RANKL). In opinion of Lipton et al. [5], the elevations of circulating OPG in serum of patients with malignancy are not high enough to uniformly suppress osteoclast formation [5]. In our study, the levels of OPG were significantly higher in lung cancer patients than those in the controls. On the contrary, Lipton et al. [5] showed that the levels of OPG in lung cancer patients did not differ significantly from those in healthy volunteers. There were only 16 lung cancer patients in that study. Our study included 39 patients with lung cancer. To our knowledge, the current study is the second one to report serum OPG levels in lung cancer patients in relation to the clinical stage of tumour.

ProGRP has been demonstrated as a tumour marker for SCLC in the investigations of Oremek et al. [7]. In our studies, the mean serum values of ProGRP were higher in cancer patients than those in the controls. The SCLC patients had higher levels of ProGRP than the ones with NSCLC. We confirm the observations of Schneider et al. [6]. They reported that ProGRP was a good tool for discriminating NSCLC versus SCLC [6]. SCLC differs clinically and biologically from NSCLC types. The incidence of distant metastases of SCLC at the time of primary diagnosis is very high. In our studies, no significant differences of ProGRP were noted in relation to the NSCLC clinical stage. In accordance with the literature [6], ProGRP reached more elevated serum levels in patients with limited disease. Thus, serum levels of ProGRP could be used to discriminate between extensive disease SCLC versus limited one.

The expression of OPG protein in gastric carcinoma tissues correlates with the clinical stage of the tumour [4]. In our study, the mean OPG level in patients with Stage IV was significantly higher than that in patients with Stage IIIB. The same observations were made by Lipton et al. [5]. They noticed a trend towards higher levels of OPG in patients with metastatic disease, compared to those with localized malignancy [5]. Those observations confirm that different mechanisms are responsible for OPG increase in serum of lung cancer patients. OPG is a factor derived from tumour and bone [8]. In the studies by Eaton et al. [8], there has been a conclusion that OPG is a potential new marker, which is elevated in serum of patients with advanced prostate cancer. Our results, based on lung cancer patients, are in agreement with the studies by Eaton et al. [8].

In our studies, there were no significant differences in either OPG or ProGRP with respect to the response to applied therapy. To our knowledge, the current study is the first one to report serum OPG in relation to the response of lung cancer to applied therapy. Eaton et al. [8] showed that, in a prostate cancer group, OPG was an indicator of the disease progression. We did not confirm these observations in our patients with lung cancer.

ProGRP has been demonstrated as a promising tumour marker for SCLC monitoring [4]. Tumour markers may represent the total body tumour load. Rising tumour marker concentrations in lung cancer patients may indicate tumour progression, which may help avoiding the continuation of ineffective treatment. In our studies, the levels of ProGRP in progressed patients were the same as those in responder ones.

Concluding, the measurements of OPG and ProGRP can be useful in clinical practice. Their clinical significance in the monitoring of chemotherapy and for the prognosis of lung cancer needs further studies.

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