RESEARCH ARTICLE

Is there any Potential Clinical Impact of Serum Phosphorus and Magnesium in Patients with Lung Cancer at First Diagnosis? A Multi-institutional Study

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Abstract

Background: The aim of the study was to determine whether the expression of baseline phosphorus (P) and magnesium (Mg) levels were prognostic in terms of stage and overall survival (OS) in newly diagnosed non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) patients. Materials and Methods: Retrospectively, 130 patients were selected at the time of diagnosis oflung cancer (100 with NSCLC and 30 with SCLC), before the initialization of any chemo-radiotherapy. The median age was 67 (range 29-92). IA, IB, IIA, IIB, IIIA, IIIB and IV stages were present in 3, 4, 19, 6, 25, 8, and 65 patients, respectively. After centrifugation, the levels of serum P and Mg were measured using the nephelometric method/ photometry and evaluated before any type of treatment. Results: Higher than normal levels of P were found in 127/130 patients, while only four patients had elevated Mg serum values. In terms of Spearman test, higher P serum values correlated with either stage (rho=-0.334, p<0.001) or OS (rho=-0.212, p=0.016). Additionally, a significant negative correlation of Mg serum levels was found with stage of disease (rho=-0.135, P=0.042). On multivariate cox-regression survival analysis, only stage (p<0.01), performance status (p<0.01) and P serum (p=0.045) showed a significant prognostic value. Conclusions: Our study indicated that pre-treatment P serum levels in lung cancer patients are higher than the normal range. Moreover, P and Mg serum levels are predictive of stage of disease. Along with stage and performance status, the P serum levels had also a significant impact on survival. This information may be important for stratifying patients to specific treatment protocols or intensifying their therapies. However, larger series are now needed to confirm our results.

Keywords: Phosphorus - Mg - serum levels - lung cancer - diagnosis - prognosis - stage - overall survival

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Introduction

Lung cancer represents the first cause of oncologic death in USA. In 2012 approximately 226.000 new cases were diagnosed and 160.000 deaths occurred (Siegel et al., 2012). Only 15.9% of all patients will be alive 5 years after diagnosis (Howlader et al., 2009). However there was much progress has been made in the last years in screening, diagnosis and treatment (Ettinger 2012).

Phosphate is vital to normal physiologic functioning; it plays a role in intracellular signaling, membrane function, energy metabolism, and bone mineralization (Sommer et al., 2007). The selective uptake of 32 P by cancer cells has been known since 1940 by Marshak et al. (1940). Several investigators confirmed this finding (Kenney et al., 1941; Marinelli et al., 1942; Low Beer 1946). Papaloucas, several years ago, found that the malignant tissue takes up approximately six times more 32P than the normal tissue, while in patients with a poor response to treatment there was a high uptake of 32P (Papaloukas, 1958).

Magnesium is the second most abundant intracellular element in the body, involved with over 300 biological activities (Seri and French, 1984). Magnesium plays an essential role in DNA repair, cell differentiation and

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proliferation, apoptosis, and angiogenesis (Seri and French, 1984; Bussiere et al., 2002; Wolf et al., 2007). Dai et al found that low blood Mg levels were associated with high-grade prostate cancer (Dai et al., 2011).

In a wide research in the PubMed/MEDLINE, there was found no other study appraising the values of P and Mg in the serum of cancer patients. The aim of the present study was to investigate any potential clinical impact of P and Mg serum levels at first diagnosis of lung cancer.

Materials and Methods

Pre-treatment work-up

In a retrospective way we selected 130 patients with lung cancer who were referred in three University Radiotherapy departments for chemo-radiotherapy (radical or palliative). All 130 patients presented with respiratory symptoms as cough, dyspnea, hemoptysis, postobstructive pneumonia and pain. They were assessed by history, clinical examination, including performance status, weight loss, smoking and alcohol status. The laboratories included CBC, BUN, Cr, LFTs, alkaline phosphatase, LDH. The imaging tests were CT chest and abdomen (to rule out adrenal or liver metastasis) ±PET scan. Lesions suspected of being tumors were then biopsied. The diagnosis of the malignancy was confirmed using cytology and histopathology after taking samples from the primary malignancy.

Study design-involvement criteria

The main purpose of the study was to measure the P levels in the peripheral blood of lung cancer patients before any treatment and correlate them with overall survival. At presentation in the radiotherapy departments, all the participating patients had filled a general informed consent which covered the potential use of their initial blood samples for assessing the levels of serum P and Mg. In a retrospective way, we selected from our database the patients that confirmed to the following inclusion criteria: *a)* ECOG performance status 0 to 2 at diagnosis; *b)* Diagnosed and histologically confirmed Non-Small Cell Lung Cancer and Small Cell Lung Cancer; *c)* No history of chemotherapy or radiotherapy treatment before measurement; *d)* No co-morbidities related to hyperphosphatemia.

Finally, 130 patients with a diagnosis of lung cancer were en¬rolled in the present retrospective study in a median time of approximately 5 years. The patients' characteristics are shown in Table 1. The staging was performed according to the TNM System of American Joint Committee on Cancer (AJCC, 2010).

Anticancer treatment

A CT-scan in supine position of 5 mm thickness was made without and with contrast (due to its effect to the tissue heterogeneity that requires correction). The tumor targets were defined according to the ICRU reports 50, 62. (ICRU 50,62) Clinical Target Volume (CTV) was defined as the primary tumor, the affected lymph node and the increased metabolic activity in PET scan. The planning target volume (PTV) was the CTV plus margins for set up error, inaccuracies of everyday positioning and movement of internal organs. In all cases the radiotherapy technique used was the 3-Dimensional Conformal Radiotherapy (3DCRT). The procedure was performed using a linear accelerator and were applied energies of 6 to 15 MV, in order to make effective the dose distribution. The treatment planning was performed using either the Eclipse™ treatment planning system (Varian Medical Systems, United States) or the PLATO (Nucletron, The Netherlands). In case of radical irradiation a prescription dose of 60Gy was used. Otherwise, in case of palliation, a schedule of 2x850Gy was given. (Plataniotis et al., 2002). A special care in order to keep the dose as low as possible to the normal lung tissues was given to avoid radiation induced toxicity in terms of radio-pneumonitis (Kouloulias et al., 2013).

Chemotherapy was also given to the participated patients, according to the current NCCN® (National Comprehensive Cancer Network) guidelines (NCCN, 2014).

Measurement of serum P and Mg

A peripheral blood sample was obtained before starting of indicated therapy and the values of Mg and P were tested. The samples were centrifuged and serum P and Mg were measured, using the nephelometric method (Beckman Coulter, Image Immunochemistry System, U.S.A.) / photometric method. The values considered as normal were the following: P (2.4-4.1 mg/dL), Mg (1.7-2.2 mg/dL).

Follow-up

The patients' follow-up at two-month intervals included: medical history, clinical examination, hematological and biochemical testing, thoracic and upper abdominal CT-scan, with contrast. Time to death from diagnosis was assessed as overall survival (OS). The cause of death for all patients was the primary disease (lung cancer).

Statistical analysis

Differences of P and Mg levels from the normal ones were assessed with the Mann-Whitney test. Correlations of P and Mg serum levels with either stage or OS were performed with the spearman-rho non-parametric test. The significance level was set at 0.05. For assessing the potential impact to overall survival of all relevant factors, we performed a cox-regression survival analysis. The cox regression was conducted in two stages. In stage one, a univariate cox-regression analysis was estimated individually each possible significant factor. In stage two, all significant dactoras from univariate analysis were entered into a forward stepwise selection routine (likehood ratio criterion, chi2 model p for entry=0.05). The whole analysis was performed with the SPSS ver 10 software (IL, USA).

Results

High levels of P were found in 127/130 patients, showing a significant deviation from the normal values

(p<0.001, 95%CI 3.04-3.66; Mann Whitney test).. However only in four patients there was an elevated value of serum Mg (p=0.89, Mann-Whitney test). Moreover, in terms of spearman test, there was a negative correlation of P values with stage (p<0.01) and survival in days (p=0.016) (Table 2). Additionally, a significant negative correlation of Mg serum levels was found with stage of disease (p=0.042), but not with OS (p=0.445) (Table 2).

The cox-regression analysis is shown in Table 3. The univariate cox-regression analysis showed that age, smoking, stage, PS, and phosphorous had a significant impact (p<0.05). However, in multivariate analysis, age and smoking lost their prognostic value, while the analysis revealed that only stage, PS and P had a significant impact to overall survival.

Table 1. Clinical Characteristics of the Patients

Median age (range)		67 (29-92)
	Male / female	115/15
	Smoking	
	No / Yes	7/123
	Alcohol	
	No /Yes	53/77
ECOG status	0	41
	1	59
	2	30
Type of cancer	Adenocarcinoma	50
	Squamous	42
	Large-cell	8
	SCLC	30
Grade	I	15
	II	43
	III	72
Stage	IA	3
	IB	4
	IIA	19
	IIB	6
	IIIA	25
	IIIB	8
	IV	65

Table 2. Spearman Rho Correlations (P: Significance Level) of P and Mg Levels with Stage of Disease and Overall Survival (OS)

		Phosphorous	Magnesium	OS (days)
Stage	Rho	-0.334	-0.135	-0.508
	P	<0.001	0.042	<0.001
Phosphorous	Rho		0.237	-0.212
	P		<0.001	0.016
Magnesium	Rho			0.045
	P			0.445

Table 3. Univariate and Multivariate Cox-regression Survival Analysis for OS (days) in Terms of Age, Smoking (Packets Per Year), Performance Status (PS), Stage, Pathology (Adenocarcinoma, Squamous, Large Cell or Small Cell), Phosphorous (P) and Magnesium

Parameter	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95%CI)	p	Odds Ratio (95%CI)	p
Age	1.11 (1.01-1.28)	0.037	-	0.12
PS	2.02 (1.53-2.65)	<0.01	2.10 (1.67-2.75)	<0.01
Pathology	-	0.348		
Smoking	1.07 (1.01-1.13)	0.044	-	0.1
Stage	1.75 (1.28-1.71)	<0.01	1,47 (1.29-1.67)	<0.01
P	1.13 (1.02-1.21)	0.024	1.08 (1.02-1.17)	0.045
Mg	-	0.78		

*CI: confidence interval

Discussion

By all means, a simple laboratory test stands always in need for evaluating prognosis in lung cancer. (Kaya et al., 2013; Song et al., 2013) The hyperphosphatemia in general is associated with several clinical situations: transplanted organs/tissues, renal failure, addictions of anaesthetics/ narcotics, feverish conditions, trauma, bone fractures, osteomalacia, pregnancy, hypoparathyroidism, hormone users, inflammation, liver cirrhosis, heavy smokers and alcoholics. It has been shown some of those conditions may influence, sometimes, the amount of phosphorus in the blood and give false results (Pertzoff and Gemmill, 1949; Sorensen et al., 1998; Spira et al., 2004; Podd, 2010). In our study it was confirmed that none of our patients had the above mentioned co-morbidities.

Cobanoglu et al. (2010) found that there was a negative correlation between Mg levels in 30 lung cancer patients and 20 healthy human. The Mg value measured in lung cancer group was significantly lower than the control group. Demir et al. (2011) found levels of Mg to be lowered in patients with leukemia (p=0.011). Leone et al. (2006) in a prospective study of 4035 men noted that high magnesium values at baseline were negatively related for cancer related deaths. Dai et al. (2011) reported that elevated Mg was significantly associated with a lower risk of high-grade prostate cancer, while an elevated Ca/Mg ratio was also associated with an increased risk of high-grade prostate cancer. Our results are in accordance with the above observations, since elevated Mg values were negatively correlated with the stage of disease.

Inorganic P is a vital component of nucleotides, membrane phospholipids, and phosphorylated intermediates in cellular signaling. Cancer cells that proliferate rapidly, require a high amount of ribosome and other P-rich RNA components that are necessary to manufacture proteins (Kenney et al., 1941; Marinelli et al., 1942; Low-Beer 1946; Papaloukas, 1958). Consequently it is a theoretical belief that tumor cells are richer in phosphorus than the surrounding tissue, and that they are promoting their metastasis due to their nutrient demands (De Carvalho and Caramujo, 2012). Since tumor cells typically up-regulate ribosome biogenesis, it would be expected that the fastest growing cancer cells would reach a plato in terms of P concentration. Indeed, a mathematical model developed by Bertuzzi et al. showed that a decrease in the phosphorus uptake of tumor cells to half, may lead to a three quarter reduction in tumor size (Bertuzzi et al., 2002). De Carvalho et al. (2012) showed that cancer cells require high amounts of P in order to maintain their high growth rate and to proliferate as well as to metastasize. A primary tumor is formed by genetically and physiologically different cell subpopulations that compete among themselves and with the surrounding healthy cells for resources that include oxygen and nutrients (Bertuzzi et al., 2002). The microenvironment of tumor cells becomes

P-depleted, driving possibly cancer cells to redirect P to essential molecules through the increase of phosphatases, resulting in an increase of the P uptake by increasing the number of transporters (Gryshkova et al., 2009). Finally, there is an increase of the site vascularization through angiogenesis, while new locations are generalized through metastases and colonizing.

Elser et al. (2007) indicated that high P demands of proliferating tumors affect the homeostasis of the human body. Oncological hypophosphatemia and tumor-induced osteomalacia could be a clinical reflection of the use of serum phosphate by cancer cells (Kumar, 2000; Amanzadeh and Reilly, 2006). Moreover, the increase need for phosphoriliosis of intracellular proteins (a typical phenomenon related to cancer) is pushing faster-growing cells into more aggressive behavior and metastatic potential, thus into more advanced stage of disease (Kuang et al., 2004). In fact, the more tumorous mass the less P-serum levels in the blood, since the fast-growing cells are getting more P in the intracellular environment. Consequently, in early stage the phosphorous in increasing in the blood, while in advanced stage the phosphorous is decreasing due to the increasing intracellular need, but still remaining over the normal limit. This might be the possible explanation for our findings, concerning the negative correlation of the P-serum levels with the stage and survival: higher in early stage, lower but still abnormal in the advanced stage.

Our results showed two main aspects, in terms of clinical impact. First, higher than the normal P serum values might be a simple screening test for the pre-clinical diagnosis of lung cancer. Papaloucas et al. have already suggested the serum level of phosphorous as a simple test for the existence of cancer somewhere in the human body (Papaloucas et al., 2013). Secondly, it seems that as the cancerous load is increasing, the P values are lower but still over the normal values. This remark is in accordance with the previous publications of Papaloucas and De Carvalho et al., that the tumor is up taking the inorganic phosphorous from the blood during its progression (Papaloucas, 1958; De Carvalho et al., 2011). Thus beyond a simple screening test for the diagnosis, the P serum values might also be a prognostic factor for therapeutic strategies for lung cancer patients. This clinical remark should not be underestimated, while more patients are needed for the extraction of safe results. In a parallel way, the Mg serum values seems to be correlated with the stage of disease for lung cancer patients.

At last but not least, the multivariate analysis showed also a significant (p=0.045) prognostic value of P serum levels. The stage and PS also had a significant impact, which is in accordance with several publications (Babacan et al., 2014; Inal et al., 2013; Oven Ustaalioglu et al., 2013). Arslan et al. (2014) among 122 non-small lung cancer patients with advanced stage showed that age, PS and stage were independent prognostic factors for survival. Reck et al. (2012) together with Firat et al. (2012) have already reported the significance of poor PS to survival. However, according to our knowledge, this is the first study reporting on the significant impact to survival of P serum levels in terms of a cox-proportional survival model.

In conclusion, the values of P and Mg are easily obtainable biomarkers that can be related to outcome in lung cancer patients, helping the clinicians to manipulate and plan the upcoming treatment strategy, while the P serum level seems that represent a novel prognostic factor for lung cancer patients. At last but not least, the P serum values might represent a simple screening test for the pre-clinical diagnosis of lung cancer patients. However, it should be mentioned that more patients included in a prospective trial are needed for the extraction of safe conclusions.

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