Determination of Soluble HER-2/neu (sHER-2/neu) in Iranian Patients with Lung Cancer

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ABSTRACT

Background: The HER-2/neu gene is located on chromosome 17q21 and encodes a 185-kDa transmembrane glycoprotein with tyrosine kinase activity reported to be released in soluble form in various malignancies. **Objective:** To evaluate the clinical significance of soluble Her-2/neu as a diagnostic marker in lung cancer. **Methods:** Serum levels of soluble HER-2/neu were measured in 43 patients with lung cancer and 42 age and sex matched controls by an enzyme immunoassay method. **Results:** Mean serum level of soluble Her-2/neu in cancer patients was 6.07±10.37 ng/ml which was significantly higher than the control group ($P < 0.05$). Cigarette smoking had no effect on the level of soluble HER-2/neu. A cut off value of 6.1ng/ml revealed a high specificity (95%) for diagnosis of lung cancer, but a very low sensitivity (14%). **Conclusion:** The results of this study show an increased level of soluble HER-2/neu in the sera of lung cancer patients with a high specificity but low sensitivity for diagnosis of lung cancers.

Keywords: Lung Cancer, HER2/neu, Iran

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INTRODUCTION

$ErbB_2$ (HER-2/neu) is a 185KDa glycoprotein with tyrosine kinase activity. The implications of HER-2/neu in mammary carcinogenesis have been investigated in vitro and in vivo. Several studies on $ErbB_2$ have been carried out on breast cancer patients (1-3), and in different types of human malignancies notably: ovarian, gastric, pancreatic, prostatic, colorectal, female genital tract, head and neck, liver (4-6), and also lung cancer (1, 7-14).

Some studies have shown that a small subset of non-small cell lung cancers (NSCLC) overexpress HER-2/neu. Nevertheless, the exact percentage of HER-2/neu overexpression in lung cancer is variable, ranging from 5% to 64% (5,8,9). Even in some patients elevated serum protein levels were detected prior to clinical diagnosis (8). This study was designed to assess the level of HER-2/neu in Iranian patients with lung cancer.

SUBJECTS AND METHODS

Studied Population. Present study was a cross sectional study enrolling patients who were referred to a tertiary hospital in the south of Iran, between April 2002 and September 2003. Each patient with clinical suspicion of lung malignancy was evaluated by chest X-ray, lung CT-scan, diagnostic bronchoscopy, and biopsy of the suspicious lesion. Forty three out of 92 patients had definite diagnosis of lung malignancy. A control group consisting of 42 subjects with matched age, sex, and smoking history. All control individuals were asymptomatic who had a normal chest X-ray. The characteristics of case and control groups are shown in Table1.

Table 1. Characteristics of 43 lung cancer patients and 42 controls

	Lung Cancer		Control	
	Number	**Percentage**	**Number**	**Percentage**
Sex				
Male	35	81.4	35	83.3
Female	8	18.6	7	16.7
Age (Mean ± SD)		65.9 ± 8.9		63.4 ± 6.7
Smoking				
Non-smoker	7	16.3	6	14.3
Smoker	38	83.7	36	85.7

The mean age of the patients and controls were 65.9±8.6 and 63.4±6.7 years, respectively. Based on a detailed questionnaire, demographic data, smoking history, occupation, family history of cancer, and health status of both groups were recoded. 83.7% of the lung cancer patients were smokers also 85.7% of controls were smokers. Among smokers, the mean pack year of smoking was 40.1±9.2 in neoplastic patients and 34.3±5.8 years in controls.

Among patients with lung cancer, 32 (74.4%) had squamous cell carcinoma (SCC), 9 (20.9%) had small cell lung cancer (SCLC), and 2 (4.7%) had adnocarcinoma.

Determination of sHER-2. Blood samples from all individuals were collected by venipuncture, sera were separated by centrifugation, and stored at -20°C.The HER-2/neu concentration was measured by a Sandwich Enzyme Immunoassay (ELISA) (Bender Med systems, Austria).

Statistical Analysis. SPSS 11.5 software, student T-test, and Mann Whitney test were used for comparison between groups.
Chi-square test was used to assess the association of tumor type, sex, and smoking history with SHER-2/neu positivity. In current study mean±2SD of SHER-2/neu level in the control group (i.e. 6.1 mg/ml) was used as the cut off value.

RESULTS

The serum levels of HER-2/neu in lung cancer patients and control individuals are depicted in Table 2. The mean levels were 6.07±10.37 ng/ml (range 0.2-52.6 ng/ml) in lung cancer patients and 2.71±1.67 ng/ml (range 0.2-9 ng/ml) in controls, which were found to be statistically significant ($P<0.05$). The level of HER-2/ neu in NSCLC and SCLC were 6.85±11.58 ng/ml and 3.13±1.88 ng/ml, respectively ($p>0.05$).

Table 2. sHER-2/neu levels in 43 primary lung cancers and 42 controls

	No. of cases	Mean ngr/ml	Standard deviation	Range
Control	42	2.71	1.67	0.2-9
Cancer	43	6.07	10.37	0.2-52.6
Squamous cell lung cancer	32	7.13	11.85	0.2-52.6
SCLC	9	3.13	1.88	2-8
Adenocarcinoma	2	2.4	0.56	2-2.8

Table 3 presents the mean concentration of HER-2/neu protein in lung cancer and control groups according to sex, smoking history, and tumor type. No association was found between HER-2/ neu level and sex, smoking history, and tumor type. Fourteen percent of lung cancer patients (6 out of 43) and 4.8% of control (2 out of 42) individuals showed HER-2/neu values greater than the selected cut-off point of 6.1 ng/ml. Accordingly, a high specificity (>95%) and low sensitivity was detected for the SHER-2/neu test in the diagnosis of lung cancer.

Table 3. sHER-2 / neu in lung cancer and control individuals according to some variables

Variables	Numbers		SHER-2 / neu (mean±SD)	
	Lung cancer	Control	Lung cancer	Control
Sex				
Male	35	35	6.75± 11.38	2.71±1.77
Female	8	7	3.1±2.01	2.71 ± 1.18
Smoking				
Non-smoker	7	6	8.2±9.37	2.75 ± 1.38
Smoker	36	36	5.66±10.57	2.71 ± 1.74
Type of tumor				
Squamous cell	32		7.13 ± 11.85	
Adenocarcinoma	2		2.4 ± 0.56	
Small cell lung cancer	9		3.13 ± 1.88	

DISCUSSION

Several studies have shown that HER-2/neu oncogene is overexpressed in different tumors and its encoded protein is released and can be detected in sera of neoplastic patients (5). Considering HER-2/neu overexpression in lung cancer (SCLC and

NSCLC), several reports with inconsistent results, particularly due to different techniques and/or heterogeneous populations examined have recently been published (7,15). HER-2/neu positivity has been reported to be a marker for poor prognosis in lung cancer (5,7,10,16-20), causing resistance to chemotherapy and leading to herceptine therapy (17,21,22). Therefore detecting its over expression may play a role in identifying patients at risk of decreased survival and drug resistance.

The sensitivity of this marker in lung cancer is still controversial (5-64%). A low sensitivity was observed by Filiberti.R (1) and a high sensitivity by Brandt-Rauf P.W. (8).

We analysed sHER-2/neu in lung cancer patients and found an increased value in 14% of the patients. Although it was in agreement with some studies (20), others reported lower or higher values compared to our results (23-26). These differences could be explained by low percentage of adenocarcinoma, with greater expression of sHER-2/neu (5%), compared with squamous cell carcinoma in the studied group (1, 2, 27-31). Another explanation is the geographic or ethnic variations among studied populations. However this low sensitivity was accompanied by a high specificity.

In agreement with other publications, we did not find any correlation between HER-2/neu levels and tumor histiotype, history of smoking, and sex of the patients (1,7).

HER-2/neu overexpression in SCLC has been investigated in few reports. Although previously overexpression of HER-2/neu in SCLC was postulated to be only of minor clinical relevance compared to NSCLC, in our study levels of HER-2/neu were the same in both groups. Due to small number of samples, the true prevalence could not be determined.

In conclusion, our results suggest that detection of SHER-2/neu in sera of patients can not be considered as a reliable indicator for screening or diagnosis of lung cancer. However due to the high specificity of the marker in these patients, it might be a reliable co-diagnostic marker in high risk individuals. It is also interesting to determine if combination of other highly sensitive markers such as carcinoembrionic antigen (CEA), neuron specific antigen, and tissue polypeptide specific antigen with SHER-2 /neu molecule could provide a better diagnostic tool in lung cancer (32-35).

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