Evaluation of a new tumour marker in patients with non-small cell lung cancer: CYFRA 21-1

Thesis

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بسم الله الرحمن الرحيم

{ قالوُا سبْحَانَكَ لا عِلْمَ لَنَا إلا َ مَا عَلَّمتَنَا إنكَ أنْتَ العَلِيمُ الحَكِيم ُ }

صدق الله العظيم

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LIST OFABBREVIATIONS

AC: adenocarcinoma

ACS: American cancer society

ACTH: adrenocorticotropic hormone

AFP: Alpha fetoprotein

AJCC: American Joint Committee on Cancer

ANITA: Adjuvant Nalvelbine International Trialist Association Trial

ASR: age-standardized incidence rate

BB: Bombesin

CEA: carcinoembryonic antigen

CK: cytokeratin

CNS: central nervous system

COL: collagen

EAS: ectopic ACTH secretion

ELISA: Enzyme-linked immunosorbent assay

hCG: human chorionic gonadotropin

IALT: International Lung Cancer Trial

IGF: insulin like growth factor

IRMA: immunoradiometric assay

LC ESI-MS/MS: liquid chromatography electrospray ionisation-mass spectrometry

LDH: lactate dehydrogenase

MALDI TOF/MS: matrix assisted laser desorption ionization time of flight mass spectrometry

MECC: middle east cancer consortium

NCAM: neural cell adhesion molecule

NSCLC: non-small cell lung cancer

NSE: neurone specific enolase

OR: objective response

Or: Odd's ratio

QOL: quality of life

RCT: randomized clinical trial

ROC curves: receiver operating characteristics curves

SCC: squamous cell carcinoma

SCC-ag: squamous cell carcinoma antigen

SCLC: small cell lung cancer

SIADH: syndrome of inappropriate secretion of antidiuretic hormone

sIL-2R: serum interleukin-2 receptor

TAA: tumor associated antigen

TLC: total leucocytic count

TNM: tumor node metastasis

UICC: Union for International Cancer Control

US SEER: United States surveillance epidemiology and end results

Abstract

Lung cancer is one of the most common fatal malignancies. Cyfra 21-1 is a tumor marker based on the determination of water-soluble cytokeratin 19 which is secreted by normal or malignantly transformed epithelial cells. It is suggested to be a valuable marker in the diagnosis of patients with lung cancer especially non-small cell type (NSCLC). This study was performed on 41 lung cancer patients, 19 patients with lung disease and 20 normal controls. Serum Cyfra 21-1 was measured by Enzyme Linked Immunosorbent Assay (ELISA). Serum Cyfra 21-1 was significantly increased in patients with lung cancer ($p=0.000$), especially in NSCLC ($p=0.010$) compared to SCLC. A significant positive correlation ($r=0.506$) was detected between serum CEA and serum Cyfra 21-1. Cyfra 21-1 showed a significant association ($p=0.010$) to lung cancer risk development in a logisitic regression analysis. Cyfra 21-1 is a tumor marker, with high sensitivity (82.5%) in NSCLC and is valuable in the diagnosis and differentiation of lung cancer.

Keywords: lung cancer, Cyfra 21-1, non small cell lung cancer.

INTRODUCTION AND AIM OF THE WORK

Lung cancer is the most common cause of cancer-related death in men and the second most common in women ***(WHO, 2004)***. It is responsible for 1.3 million deaths annually ***(WHO, 2006).***

Lung cancer varies in incidence and mortality among countries, but in Middle Eastern countries it is ranked number one, and was number three in North African countries ***(Globocan, 2002).*** It is number one in cancer incidence in seven of thirteen Arab countries ***(Salim et al., 2009).*** However, lung cancer is on the rise in those countries and its health toll will mirror, and even may exceed, that of Western countries if tobacco control is not properly addressed ***(Jazieh et al., 2010).***

In Egypt, lung cancer is the fourth most common cancer in men and ninth in women. According to the Gharbia Cancer registry, it represents 7.4% of male and 2.7% of female malignancies. The Egyptian National Cancer Institute data show that the frequency of lung cancer was not different between 2001 and 2006 ***(NCI, 2006).***

Lung cancer is classified clinically as non-small cell lung carcinoma (87%) and small cell lung carcinoma (13%) for the purposes of treatment. Non-small cell lung carcinoma (NSCLC) is improved by chemotherapy following surgery, while small cell lung carcinoma (SCLC) usually responds better to chemotherapy and radiation ***(American Cancer Society, 2006).***

Potential usages of tumor markers include screening, differentiation of benign from malignant disease, histological differentiation and defining prognosis. These goals have generated considerable interests in identifying predictive tumor markers over the past three decades ***(Chapman et al., 2007).***

In malignant epithelial cells, activated protease increases degradation of cytokeratin; this results in release of large amounts of cytokeratin fragments into the blood ***(Wu et al., 2002).*** The Cyfra 21-1 assay was developed to measure a soluble fragment of cytokeratin 19 in serum). It has reported the highest diagnostic sensitivity in all types of non-small cell lung cancer (NSCLC), particularly squamous cell tumors ***(Malati, 2007)*** and in monitoring antineoplastic therapy ***(Ardizzoni et al., 2006).***

It was reported that Cyfra21-1 might be a useful tumor marker to discriminate benign from malignant pleural effusion an increase in the mean value of Cyfra 21-1 in the serum and pleural fluid of patients with malignant pleural effusion than that of patients with non-malignant effusion ***(Abd El Ghaffar et al., 1999: Shirit et al., 2005).***

AIM OF THE WORK

The aim of the present study was to evaluate serum Cyfra 21-1 as a tumor marker in diagnosing of lung cancer patients. We also studied the ability of Cyfra 21-1 to differentiate between NSCLC (including both subtypes) and SCLC. Since, CEA is thought to behave similarly to Cyfra 21-1 and that, between them, the two markers are correlated strictly, so we compared the performance of the CEA and Cyfra 21-1 in the Egyptian lung cancer patients.

LUNG CANCER

Lung cancer is one of the most prevalently occurring and the most life-threatening neoplasia in most parts of the world ***(Granville and Dennis; 2005)***. It has an incidence of 1.2 million people in worldwide and accounts for about 25% of all cancer deaths ***(Jemal et al; 2006).***

In the majority of developed countries, lung cancer is the most commonly diagnosed neoplasm in males and the second– after breast cancer – most frequent cancer in females. Lung cancer is the most common cause of cancer mortality in males and females worldwide ***(Skuladottir and Olsen; 2002).***

Lung cancer is the second most frequent cancer in both males and females in the United States after breast and prostate cancer; and the most common cause of death from cancer in men and women ages 40 and 60 years, respectively ***(Jemal et al; 2007).*** Incidence of lung cancer has decreased significantly by 1.8% per year from 1991 to 2005 among men and increased significantly by 0.5% per year from 1991 to 2005 among women. Lung cancer death rates for U.S. women are among the highest in the world. Death rates for U.S. men are lower than rates among men in several other countries, although rates among males are still higher than rates among females in the United States **(Ries et al; 2005).**

In Europe, lung cancer accounts for 21% of all cancer cases in males and 29% of all cancer deaths. The rapid increase in lung cancer incidence had been observed since the beginning of the 20th century until 1990–1994 ***(Skuladottir and Olsen;***

2001). The incidence in males has decreased, but it is still increasing in females, especially in young women ***(Leinert et al; 2000).***

The overall ASRs (age-standardized incidence rate) were much lower in the MECC (Middle East Cancer Consortium) populations than in US SEER (United States surveillance epidemiology and end results). The rates in Israel (Arabs and Jews) were approximately half that of US SEER. In Cyprus, Jordan, and Egypt, rates were between one-third and one-fifth of the US SEER rate. Among males, the lung cancer ASR in MECC populations was highest in Israeli Arabs, followed by Israeli Jews, Cypriots, Jordanians, and Egyptians. The female ASRs in Algerians and Omanians were somewhat lower than in Jordanians, Egyptians and Israeli Arabs, but Kuwaitis had a slightly higher rate ***(Al-Kayed and Qasem; 2005).***

Changes in the frequency of various histological subtypes of lung cancer occurrence are observed. Adenocarcinoma has become the most common subtype in both genders ***(Travis et al; 1995).*** Despite many clinical trials, modern diagnostic techniques and improved supportive care, the prognosis remains unfavorable. Long-term survival has almost not changed in the previous years ***(Welch et al; 2000)*** and only about 5–10% of patients survive 5 years since diagnosis ***(Ann Oncol; 2003).***

The natural history of the different types of lung cancer, other than a generally fast and fatal progression, is actually unknown. This is particularly obvious for the adenocarcinomas, in which a single TNM (Tumor Node Metastasis) stage can characterize a wide range of growth and progression. While a more precise molecular classification is awaited, a sub-classification on histological grounds seems necessary ***(Travis et al; 2006).***

Regardless of the etiology, the high incidence and poor prognosis of lung cancer make this disease a major health problem worldwide. Patients who survive one primary cancer are at considerably higher risk of a second malignancy. Current evidence suggests that the annual incidence of second primary lung cancers is in the range of 1% to 2% ***(Rubins et al; 2007 & Trousse et al; 2007).***

A second primary lung cancer is potentially curable by surgical resection if discovered early and if the initial primary is also cured. Distinguishing patients who are at higher risk to develop multiple lung tumors is of great clinical relevance. Moreover, risk factors that are identified for a second primary lung cancer are highly likely to be risk factors for lung cancer in general. Thus, studies of factors that differ significantly between patients with second primary lung cancer and patients with a solitary lung cancer are convenient vehicles for identifying new risk factors for the disease ***(Begg and Berwick; 1997).***

All these problems associated with lung cancer led to a need for updating guideline recommendations for the diagnosis and management of this neoplasm ***(Alberts; 2008).***

Risk factors for lung cancer include:

Aging and sex:

The risk of death from lung cancer increases with age and is greater in men than in women ***(National center for health statistics; 2005).***