Study of Some Tumor Biomarkers for Diagnosis of Lung Cancer in Egyptian patients

Thesis

Submitted for Master Degree in Pharmaceutical sciences
(Biochemistry)

Presented By

Mahmoud Gomaa Mohamed Yossif Eldeib

B.Sc. of Pharmacy, Al-Azhar University, 2008
Demonstrator of Biochemistry, Faculty of Pharmacy (Boys)
Al- Azhar University

Under Supervision of

Prof. Shawkey S. Ali
Professor of Biochemistry,
Faculty of Pharmacy (Boys)
Al-Azhar University - Cairo

Prof. Mostafa M. Elshafei
Assistant Professor of Biochemistry,
Faculty of Pharmacy (Boys)
Al-Azhar University - Cairo

Prof. Amal F. M. Said
Assistant Professor of Clinical Pathology,
National Cancer Institute

Dr. Omnia E. Ismail
Lecturer of Biochemistry,
Faculty of Pharmacy
Egyptian Russian University

Biochemistry Department
Faculty of pharmacy (Boys),
Al-Azhar University - Cairo
1434 - 2013

بسم الله الرحمن الرحيم

{نَرْفَعُ دَرَجَاتٍ مّن نّشَآءُ وَفَوْقَ كُلّ ذِي عِلْمٍ عَلِيمٌ}

صدق الله العظيم

(يوسف: ٧٦)

Acknowledgment

Thanks for **ALLAH**, without his help, this work could not have been accomplished.

I would like to acknowledge and express my heartfelt gratitude to my best teacher Professor ***Shawkey S. Ali,*** Professor of Biochemistry, Faculty of Pharmacy (Boys), Al-Azhar University; who supervised, encouraged and help me through my academic program. He never accepted less than my best offer to complete this work. Thank you.

A special thanks for Dr. ***Mostafa M. Elshafei,*** Assistant Professor of Biochemistry (Boys), Al-Azhar University; for helping me to complete this work.

Really I could not find words to express my thanks for Dr. ***Amal F. M. Said,*** Assistant Professor of Clinical Pathology, National Cancer Institute; who participated with great efforts and without her; I could not complete the practical part of this work.

I would also like to warmly acknowledge Dr. ***Omnia E. Ismail,*** Lecturer of Biochemistry, Egyptian Russian University, for her guidance and continuous help.

To Professor ***Fouad Fetoh,*** the head of Biochemistry department, Faculty of Pharmacy (Boys), Al-Azhar University; thank you a lot for advising me.

Deep thanks for my collogue ***Ahmed Aglaan*** for helping me in statistical analysis of this work and continuous helps. Thanks a lot for you.

Dr. ***Fatma Kasem,*** thank you for helping me in the collection of samples in this work. My colleges in Biochemistry Department, thanks for your kind feelings toward me. I have the honor to be a member of this team.

Finally I wish to express my deepest heartfelt thanks to my father, my mother, my sisters, all of my family members and my friends for their encouragement during my life

Mahmoud Eldeib

CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Refers to
AD	Adenocarcinoma
ADP	Adenosine diphosphate
Ang-2	Angiopoietin-2
APAF-1	Apoptotic protease activating factor 1
APUD	Amine precursor uptake and decarboxylation
BAC	Bronchioalveolar carcinoma
BIR	Baculovirus IAP repeat
CEA	Carcinoembryonic antigen
CgA	Chromogranin A
CPK-BB	Creatine phosphokinase-BB
CT	Calcitonin
ECs	Endothelial cells
ECLIA	Electrochemiluminescence Immunoassay
EGFR	Epidermal growth factor receptor
HRP	Hourseradish peroxidase
IAP	Inhibitor of apoptosis proteins
LCC	Large cell carcinoma
MRI	Magnetic resonance imaging
NSCLC	Non small cell lung cancer
NSE	Neuron-specific enolase
PAHs	Poly aromatic hydrocarbons
PDECGF	Platelet-derived endothelial cell growth factor

PET	Positron emission tomography
SCC	Squamous cell carcinoma
SCC-Ag	Squamous cell carcinoma antigen
SCLC	Small cell lung cancer
TB	Tuberculosis
TMB	tetramethybenzidine
TNF-α	Tumor necrosis factor-alpha
TP	Thymidine phosphorylase
TPA	Tissue polypeptide antigen
VEGF	Vascular endothelial growth factor

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

&

AIM OF THE WORK

INRODUCTION AND AIM OF THE WORK

Lung cancer ranks top in both incidence and mortality. It can cause up to 3 million deaths annually ***(Cho, 2007)***. About 9 in 10 patients diagnosed with lung cancer will die in the following two years because lung cancer was always detected in the late carcinogenesis process. Detecting lung cancer at an early and curable stage can improve survival substantially and 70% of patients who are diagnosed early can survive 5 or even 10 years ***(Henschke et al., 2006)***.

Chest radiograph and low-dose helical computed tomography screening can detect early lung cancer, but also produce some false-positive results and unnecessary invasive diagnostic procedures and treatments ***(Oken et al., 2005)***.

Ideally, diagnostic procedures should be conducted rapidly, and staff and equipment cost should be kept to a minimal level with limited complications for the patient. This rationale supports the need for identification of circulating tumor biomarkers by highly specific and accurate blood tests that can be performed at any medical facility ***(Schneider, 2006)***.

Scientists strive to explore biomarkers and their possible role in the diagnosis, treatment and prognosis of lung cancer. Researchers are trying to develop better screening and treatment options in the fight against the malignancy, as well as searching for proteins that may serve as biomarkers to detect and locate incipient lung cancer, serve as possible drug target, monitor response to therapy and predict the chance of recurrence after treatment has ended. The general strategy is to extract proteins from blood, tissue or body fluid, analyze them to discover differences that can distinguish the lung cancer patients from the healthy controls or the patients who respond to therapy versus those who do not respond ***(Cho, 2007)***.

The ultimate goal is to discover biomarkers for lung cancer that can be tested in clinical trials and finally applied to patient care.

The present study has been designed for measurement of Survivin, Angiopoietin-2 (Ang-2), Neuron Specific Enolase and Carcinoembryonic Antigen (CEA) in the serum of Egyptian lung cancer patients with primary sites and evaluation of their uses as markers in diagnosis of lung cancer and differentiation between its types.

REVIEW OF LITERATURE

1. Lung Cancer

1.1. Definition of cancer

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both external factors (tobacco, infectious organisms, chemicals and radiation) and internal factors (inherited mutations, hormones, immune conditions and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote the development of cancer ***(American Cancer Society, 2012)***.

1.2. Epidemiology of cancer

Cancer affects people at all ages with the risk for most types increasing with age. Overall, an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occured in 2008, with 56% of new cancer cases and 63% of the cancer deaths occurring in the less developed regions of the world. The most commonly diagnosed cancers worldwide are lung (1.61 million, 12.7% of the total), breast (1.38 million, 10.9%) and colorectal cancers (1.23 million, 9.7%). The most common causes of cancer death are lung cancer (1.38 million, 18.2% of the total), stomach cancer (738,000 deaths, 9.7%) and liver cancer (696,000 deaths, 9.2%) ***(Ferlay et al., 2010)***.

Lung cancers can arise in any part of the lung, but 90% - 95% of cancers of the lung are thought to arise from the epithelial tissue in the lining of the bronchi and also in the trachea, bronchioles and alveoli. For this reason, lung cancers are sometimes called bronchogenic carcinomas ***(Bouchard et al., 2002)***.

Lung cancer remains the most common cancer in the world, both in term of cases and deaths ***(Ferlay et al., 2010)***. Since lung cancer tends to spread or metastasize very early after it forms, it is a very life-threatening cancer and one of the most difficult cancers to treat. While lung cancer can spread to any organ in the body, certain organs