Prognostic Significance of Baseline Platelet to Lymphocyte Ratio in Patients with NSCLC, A Retrospective Analysis

Thesis

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List of Abbreviations

Abb.	Full term
ALCLs	Anaplastic large-cell lymphomas
ALK	Anaplastic Lymphoma Kinase
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CTLA-4	Cytotoxic T lymphocyte associated protein- 4
DFS	Disease free survival
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
GPS	Glasgow Prognostic Score
HR	Hazard ratio
IARC	International Agency for Research on Cancer
IC	Immune cells
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
KPS	Karnofsky Performance Status
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
NE	Neuro-endocrine
NGS	Next-generation sequencing
NK	Natural killer
NLR	Neutrophil-to-lymphocyte ratio
NOS	Not otherwise specified
NSCLC	Non small cell lung cancer
OS	Overall survival
PD-1	Programmed Cell Death-1
PFS	Progression free survival
PI3K	Phosphoinositide 3-kinase

List of Abbreviations Cont...

Abb.	Full term
PLR	Platelet–lymphocyte ratio
PS	Performance status
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SCLC	Small cell lung cancer
SIR	Systemic inflammatory response
SSc	Systemic sclerosis
T.B	Tuberculosis
TCIPA	Tumor cell-induced platelet aggregation
TILs	Tumor-infiltrating lymphocytes
TK	Tyrosine kinase
TKIs	Tyrosine kinase inhibitors
TNM	Tumor-node-metastases
TTF-1	Thyroid transcription factor 1
WHO	World Health Organization

INTRODUCTION

Lung cancer remains the most common cancer in the world, both in term of new cases (1. 8million cases, 12. 9% of total) and deaths (1. 6 million deaths, 19. 4% of total cancer cases). Although lung cancer is the most common cancer worldwide among men, it ranks second in more developed regions (490,000 cases) after prostate cancer (759,000 cases) in 2012 worldwide statistics ***(Ferlay et al., 2015).***

In Egypt, Lung cancer comes forth in ranking with crude incidence rate 8. 2% of all cases among males. The age standardized rate and crude incidence rate for lung cancer per 100,000 were; 10. 1 and 7. 6 in lower Egypt, 10. 8 and 6. 3 in middle Egypt, 6. 7 and 6 in upper Egypt Respectively ***(Ibrahim et al., 2014).***

Smoking is considered the main risk factor for lung cancer, causing more than 80% of all cases. The relative risk of lung cancer in long term smokers has been estimated to be 10-30 fold higher in smokers than in non smokers. Non smoking related risk factors include occupational exposure to Asbestos, chromium, arsenic, cadmium, and nickel as well as second hand smoke, previous lung diseases as chronic obstructive pulmonary disease and sarcoidosis, and radon exposure. In absence of such risk factors, The genetic susceptibility to lung cancer remains the only other possible predisposing parameter ***(Alberg et al., 2013).***

Lung cancer is histopathologically classified into small cell lung cancer (SCLC; approximately15%) and non small cell lung cancer (NSCLC). Furthermore, carcinoid and other rare entities need to be considered. The group of NSCLC is further categorised into adenocarcinomas, squamous cell carcinoma, large cell carcinomas, adenosquamous carcinomas, and NOS. Lung tumors can show a combination of different histotypes ***(Kerr et al., 2014)***.

Lung cancer is treated with a multidisciplinary approach involving surgical oncology, radiation oncology, and medical oncology. The choice of treatment strategy is based on biology (pathology including biomarkers, gene expression) and tumour extent/location (size and location of primary tumour, number and extent of lymph node involvement) as well as on the age, comorbidities and general health status of the patient and his/her preferences ***(Alberg et al., 2013).***

To date, disease stage based on Tumor-node-metastases (TNM) classification is the best prognostic factor ***(Vansteenkiste et al., 2014).***

In an attempt to better estimate the prognosis, many prognostic parameters have been investigated, such as performance status, weight loss, Biomarkers and other factors. EGFR mutations may be a positive prognostic factor for survival in advanced NSCLC patients treated with chemotherapy with or without erlotinib, and may predict

greater likelihood of response. Patients with KRAS-mutant NSCLC showed poorer clinical outcomes when treated with erlotinib and chemotherapy ***(Eberhard et al., 2005).***

Recently, it is widely recognized that systemic inflammatory response plays an important role in the initiation and progression of cancer. Molecular factors and biological pathways including upregulation of cytokines, chemokines and inflammatory mediators, promotion of angiogenesis, local immunosuppression, inhibition of apoptosis, and DNA damage are involved in this response and are associated with an increased risk of metastasis. There is increasing evidence that measures of the systemic inflammatory response, such as neutrophil, lymphocyte, C-reactive protein (CRP), and the Glasgow Prognostic Score (GPS), have prognostic value in a variety of cancers ***(Zhang et al., 2016).***

The platelet–lymphocyte ratio (PLR), defined as the absolute platelet count divided by the absolute lymphocyte count, has gained a lot of interest in recent years. Published data suggested that elevated PLR was an important prognostic factor in esophageal cancer, gastric cancer, renal cell cancer, and malignant pleural mesothelioma ***(Qiang et al., 2016).***

In a prospective study done by ***Sanchez-Lara, et al*** in Mexico from 2009 to 2011, on 119 patients with stage III-IV NSCLC, treated with chemotherapy, evaluating prognostic significance of baseline PLR on overall survival, using cut-off

value:150. Results were stastistically significant with HR for death:1.16, 95%CI: (0. 52-2. 50) ***(Sanchez-Lara et al., 2012).***

Another study done by ***Liu et al*** in China, retrospectively reviewed data of 210 patients with stage III-IV NSCLC treated with chemotherapy from 2001 to 2012, also evaluating prognostic significance of baseline PLR on overall survival, using cut-off value: 150. HR for death was 2. 025, 95%CI:(1. 4-2. 9) ***(Liu et al., 2013).***

However, the prognostic value of PLR in NSCLC remains uncertain. Therefore, in this study, we aimed at investigating the prognostic significance of PLR in NSCLC patients.

AIM OF THE WORK

The aim of the study is to evaluate the prognostic impact of baseline platelet to lymohocyte ratio on the outcome of patients with Non small cell lung cancer treated from January 2014 to December 2016 in Department of Clinical Oncology and Nuclear Medicine, Ain Shams University Hospitals, Cairo, Egypt.

Chapter 1

EPIDEMIOLOGY OF NON-SMALL CELL LUNG CANCER

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide. In 2014, lung cancer was the most frequently diagnosed cancer and the leading cause of cancer death in male populations ***(Edwards et al., 2014).***

Among females, lung cancer was the leading cause of cancer death in more developed countries, and the second leading cause of cancer death in less developed countries ***(Torre et al., 2015).***

In 2013 in the European Union, lung cancer mortality fell in men by 6% compared with 2009, while cancer death rates increased in women by 7%, thereby approaching male counterparts ***(Malvezzi et al., 2015).***

A significantly higher proportion of lung cancer is diagnosed in patients aged 65 and over. The median age at diagnosis is around 70 years ***(Ferlay et al., 2015).***

Data from 2012 revealed that in the USA, lung cancer represented the leading cause of cancer death in males above

the age of 40 years and in females from the age of 60 years ***(Ferlay et al., 2012).***

A subset of patients with non-small-cell lung cancer (NSCLC) presents at a younger age (<40 years), but the incidence in this population has decreased in the USA from 1978 to 2010 ***(Thomas et al., 2015).***

In Egypt, Lung cancer comes forth in ranking with crude incidence rate is 8. 2% of all cases among males. The age standaradized rate and crude incidence rate for lung cancer per 100,000 were; 10. 1 and 7. 6 in lower Egypt, 10. 8 and 6. 3 in middle Egypt, 6. 7 and 6 in upper Egypt Respectively ***(Ibrahim et al., 2014).***

Non-Small Cell Lung Cancer (NSCLC) account for 85%–90% of lung cancers, while small cell lung cancer (SCLC) has been decreasing in frequency in many countries over the past two decades ***(Jemal et al., 2012).***

During the last 25 years, the distribution of histological types of NSCLC has changed: in the USA, squamous cell carcinoma (SCC, which was formally the predominant histological type) decreased, while adenocarcinoma has increased in both genders. In Europe, similar trends have occurred in men, while in women, both SCC and adenocarcinoma are still increasing ***(Forman et al., 2013).***

The World Health Organization (WHO) estimates that lung cancer is the cause of 1. 37 million deaths globally per year, with an estimated 71% of these deaths are caused by smoking, indicating that ~400 000 deaths annually are attributed to lung cancer in lifetime never smokers. Prevalence of lung cancer in females without a history of tobacco smoking is estimated to represent 19%, compared with 9% of male lung carcinoma in the USA ***(McCarthy et al., 2012).***

Risk factors:

Tobacco smoking is still the main cause of lung cancer in most of the patients, and the geographic and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of human cancers. In countries with effective tobacco control measures, the incidence of new lung cancer has begun to decline in men and is reaching a plateau for women ***(Alberg et al., 2013).***

The relative risk of lung cancer in long term smokers has been estimated as 10- to 30-fold higher compared to non-smokers. The International Agency for Research on Cancer (IARC) has identified at least 50 carcinogens in tobacco smoke, including: the polycyclic aromatic hydrocarbons and the aromatic amines, N-nitrosamines, benzene, vinyl chloride, arsenic, chromium, radon, bismuth and polonium ***(Travis et al., 2004).***