LUNG CANCER: A DIFFERENTIAL MINI-REVIEW ON SUBTYPES

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Abstract

Lung cancer has high mortality worldwide. Small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) are the two types of lung cancer. Factors that determine why patients develop small cell or non-small cell cancer are unknown. The present article is a concise review of NSCLC and SCLC which describes the difference in both types of lung carcinoma based on risk factors, treatments, gender, molecular genetics, and chromosomal alterations. Understanding these differences should allow translation of the research in early diagnosis and therapy for improved survival of patients with NSCLC and SCLC.

Keywords: Lung cancer, risk factors, molecular genetics, chromosomal alterations, treatment.

I INTRODUCTION

Lung cancer is the most common and deadliest cancer in both men and women worldwide [1]. It is the fourth common cancer after colon, breast, and pancreatic cancers [2]. World Health Organization had classified lung cancer in two main subtypes: small cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC), accounting for 15% and 85% of all lung cancer, respectively [3]. It is highly heterogeneous in nature and named based on where it develops along the bronchial tree (Table 1). Lung cancer is an asymptomatic cancer as patients show symptoms of general cough and flu which are sometimes confused with the symptoms of tuberculosis. By the time patients reach the clinics, 70% of them are already in advanced stages. Late-stage diagnosis of lung cancer makes the applicability of surgery and radiotherapy less favourable for the treatment and hence, chemotherapeutic regimens are the preferred treatment. Significant advancement has been achieved with NSCLC treatment, particularly in adenocarcinoma (ADC) and squamous cell carcinoma (SCC). This is evident by approval of a number of treatments by FDA that include epidermal growth factor receptor (EGFR) and anaplastic lymphoma receptor tyrosine kinase (ALK) targeted therapy and, more recently, biological therapy using immune checkpoint inhibitors [4]. On the other hand, for SCLC, which is already metastatic at early stages, no effective targeted therapy has been identified as yet. First-line treatment chemotherapy in SCLC has not changed since the last decades, although promising results were obtained recently with immune checkpoint inhibitors that may improve the survival rate of SCLC patients [5]. Despite these encouraging developments in subgroups of patients, therapeutic improvement for lung cancer patients as a whole are still needed. This review describes the difference in two subtypes (NSCLC and SCLC) of lung cancer based on risk factors, treatments, gender, molecular genetics, and synteny.
RISK FACTORS

SCLC is composed of much smaller cells that rapidly metastasize to other organs much faster than NSCLC types. SCLC if untreated can be fatal in a short span of few weeks, in contrast to most cases of NSCLC with metastasis [6]. The main aetiological factor in lung carcinogenesis is tobacco consumption [7]. Smoking is the main cause of death in at least 80% cases of lung cancer [8]. The association factor of 1.14 to 5.20 was reported for developing lung cancer in people who had never smoked but lived with a smoker [9]. Almost all patients with SCLC are current or former heavy smokers [10]. NSCLC, however, has been detected in non-smokers indicating that many other environmental and occupational factors may have role to play in this disease. Various studies point towards factors such as exposure to pollutants, radon, and asbestos [11,12,13]. In addition to environmental and occupational hazards, poor diet, genetics are important contributors [14]. Mutations in oncogenes and tumor suppressor genes may also lead to lung cancer [15]. Other familial risk factors also play a role in lung cancer. SCLC female patients have shown parental history [16]. Changes in EGFR gene have been seen more often in young Asian women smokers having adenocarcinoma of the lung and excess EGFR protein has also been reported in more than 60% of metastatic NSCLCs [17]. RB1 tumor suppressor gene is thought to be important in the development of SCLC whereas, acquired changes in the p16 tumor suppressor gene and the K-RAS oncogene, are thought to be important in the development of NSCLC. Changes in the TP53 tumor suppressor gene and chromosome 3 have been reported in both NSCLC and SCLC [18,19,20].

CURRENT TREATMENTS FOR NSCLC AND SCLC

In order to determine the treatment plan, prognosis, review of improvement and further studies, cancer staging plays critical role. Staging of lung cancers is also based on International TNM criteria; T stand for size and extent of primary tumour; N indicates to what extent has tumour spread to regional lymph nodes and M is metastasis to other tissues. Combination of these criteria is used for assigning stages to NSCLC from I through IV, higher the stage, more advanced stage the cancer is.

Patients who have stage I, II, and IIIA NSCLC are evaluated for surgery using imaging and biopsies and if tumors are resectable, surgery is done to remove the tumours. Video-assisted thorascopic surgery (VATS) is done to make a small incision in the chest and a thoroscope is inserted [21]. For reducing the risk of lung cancer relapse, some patients who have undergone a resection surgery may benefit from adjuvant therapy which may include radiation, chemotherapy, and targeted therapy. Patients with stage IIA, IIB, and IIIA NSCLC usually receive chemotherapy after surgery to kill any remaining cancer cells in order to prolong survival [22]. These treatments are given to improve survival and reduce disease-related adverse effects in patients.

Cytotoxic combination chemotherapy is the first-line therapy for patients who are in advanced stages of NSCLC and have survival of 0 or 1. According to The American Society of Clinical Oncology, such patients should be given a platinum therapy (cisplatin or carboplatin) plus paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, or pemetrexed [23]. Cisplatin is slightly more effective than platinum, however, it has
been associated with more side effects. Due to its adverse effects, chemotherapy should be stopped if cancer grows and tumors are not shrinking or if, after four treatment cycles, the disease is stable [24].

SCLC has been classified in two categories, limited-stage (LS), which is confined to one hemithorax and one radiation field or extensive stage (ES) which extends beyond one hemithorax, by the most commonly used staging system the Veterans Administration Lung Study Group (VALG) staging system [25]. LS SCLC is treated with concurrent chemoradiation and the ES is treated with platinum-based (cisplatin-etoposide or cisplatin-irinotecan or cisplatin-topotecan) with or without concurrent radiation therapy, followed in general by topotecan (Hycamtin), the sole agent approved by FDA, specifically for the second-line setting [26]. Topotecan has a role in cell death as it binds to the topoisomerase I-DNA complex and prevents the relegation of DNA [27]. Standard third-line treatment is lacking although single-agent paclitaxel, irinotecan, gemcitabine, and vinorelbine are commonly tried in patients with acceptable performance status. The prognosis for relapsed SCLC is poor with a median survival of weeks to months [28]. Literature suggested that in the advanced stage of lung cancer, chemotherapy is the only treatment.

**COMBINED NSCLC AND SCLC HISTOLOGY**

Whenever a patient reaches the clinic, he is diagnosed with the detection of the type of lung cancer and then treatment strategies are suggested based on the assumption that the patient is having cancer of one subtype [29]. However, patients have also been detected with mixed cancer as they represent combined histology [30]. In advanced-stage lung cancer, patients are given chemotherapy as the only treatment for both NSCLC and SCLC, but the drugs used are distinct for each subtype.

In general, patients with extensive-stage SCLC show a greater response to chemotherapy than those with metastatic NSCLC. This leads to the inference that there are inherent differences in tumor biology of the two [31]. Pemetrexed is a preferred treatment in the case of metastatic NSCLC as SCLC patients have been reported to develop resistance to it. It is due to the expression of high level of thymidylate synthase which deactivates pemetrexed [32, 33].

Combined-histology lung cancers can make treatment decisions difficult. SCLC with a large-cell component accounts for about 10% of SCLC cases and at present, these patients are given standard SCLC chemo-therapy regimens [34]. Two large case series have investigated the frequency of tumors with combined SCLC and NSCLC histology [35, 36].

Historically, SCLC was thought to arise from neuroendocrine cells within the distal part of the conducting, whereas, adenocarcinomas are more commonly localized peripherally and were believed to originate from alveolar type II cells. However, studies in mouse models of lung cancer have yielded insights that could explain the shared ancestry of some SCLCs and NSCLCs [37].

**GENDER DIFFERENCE IN NSCLC AND SCLC**

Lung cancer is prevalent in both men and women. Small cell lung cancer (SCLC) accounts for 17%–34% of lung cancers in women in contrast with 15%–20% in men [38]. Trends in smoking have been reported in women which may result in changed lung cancer incidence and mortality in women [39,40,41]. However,
Smoking alone is not associated with this gender difference in lung cancer as a study in the United States showed that 15%-20% of lung cancers occur in never smokers. More interestingly, 70%-80% of never smokers with lung cancer are women [42]. There has been evidence that hormonal factors may play a role in the incidence of lung cancer and survival.

A study by Duma et al. showed that women with SCLC had better overall survival (OS) compared to men. Post-menopausal women had worse OS compared to pre-menopausal women [43]. The researchers have determined that the expression of estrogen receptor beta (ER-beta), which inhibits tumor growth, was lower in women than in men. P53 which is a molecular target for NSCLC is mutated more commonly in women [44]. GRPR which is also an NSCLC target is located on the X chromosome has increased expression in women and also increases the risk for lung cancer development from smoking [45].

**MOLECULAR GENETICS OF NSCLC AND SCLC**

Both tumor suppressor genes and oncogenes are responsible for genomic changes. Tumor suppressor genes are anti-oncogenes that regulate cell division and replication. Their inactivation results in abnormal growth of cells leading to cancer. Genetic mechanisms such as point mutations, chromosomal rearrangements, and mitotic recombinations, and epigenetic events like methylation of promoter regions can inactivate these genes [46]. Expression of c-erbB-2 gene; now known as ERBB2 is different in SCLC compared to NSCLC and its high expression is a prognostic factor in lung adenocarcinomas [47].

Another group of genes that are differentially expressed in lung cancer subtypes are MYC family genes; MYC, MYCN, and MYCL. These are frequently altered and involved in pathogenesis of SCLC. MYC is most frequently activated in both SCLC and NSCLC, whereas abnormalities of MYCN and MYCL only occur in SCLC. In nearly all cases, only one MYC family member is activated in each individual tumor [48].

According to a report, the frequency of amplification of MYC family genes is 18% to 31% in SCLC, as compared to 8% to 20% in cases of NSCLC [49]. Tumor suppressor genes, such as retinoblastoma 1 (RB1) and tumor protein p53 (TP53), are inactivated in the majority of patients with SCLC [50]. Another marker that differentiates SCLC from NSCLC is a Phosphatase and tensin homolog deleted in chromosome 10 (PTEN), a tumor suppressor gene NSCLC lack PTEN expression [51], whereas it is differentially expressed in SCLC where many mutations of this gene serve as a marker for detection of SCLC [52].

**CHROMOSOMAL ALTERATIONS IN NSCLC AND SCLC**

Consistent chromosome changes are thought to be indicative of critical molecular events involved in tumorigenesis. Loss of chromosomes 9 and 13 and loss of chromosome Y in males, is prominent in NSCLC [53]. The PTEN/MMAC1 gene located at 10q23.3 is deleted or mutated in lung cancer specifically in SCLC. Alterations of PTEN have been reported in 20% of SCLC cell lines and in 10% of primary SCLC samples [54]. 9p another most frequently deleted chromosome segment in NSCLC and might have a critical role [55].

Gene INK4a is located at 9p21 has been reported to be inactivated in more than 60% of NSCLC tumors but rarely in SCLCs [56]. Chromosome rearrangement of 17p resulting in loss of genetic material is profoundly seen in NSCLCs [57]. A study of Westen et al. also demonstrated loss of alleles from 17p to be a common occurrence in NSCLC [58].
THE TRANSFORMATION FROM NSCLC TO SCLC

Treatments for both NSCLC and SCLC are started assuming that patients are having one type of cancer at one time but studies have been done where patients have both at the same time [59]. Cases of transformation from one type to another are supported by various [60, 61]. Transformation of NSCLC to SCLC in EGFR mutant patients has been seen. However, such transformation has been reported to occur in lung cancers that do not have EGFR mutations [62].

It has been suggested that the transformation of NSCLC to SCLC may be a mechanism of resistance to immune checkpoint inhibitors (ICI) [63]. Awareness of this phenomenon is important, possibly regarding acquired resistance or mixed response cases. Repeat biopsies of progressing lesions after response to ICI can shed light on unexpected mechanisms of resistance to immunotherapy.

CONCLUSION

Tumor biology of NSCLC and SCLC is different and so are the available treatment options. Treatments that are available for advanced-stage NSCLC are not showing beneficial results in extended stage SCLC. The incidence of both subtypes is different based on gender, smoking history, and molecular genetics. Taken together, the data presented in this review clearly suggest that there are both common and distinct features in the major subtypes of lung cancers (SCLC and NSCLC), which are consistent with their markedly different biological and clinical features. To make an impact on mortality in the race for a cure of this devastating disease, we need to develop new strategies for early detection, prevention, and novel therapies based on understanding the basic underlying molecular genetic abnormalities that are involved in lung cancer.

REFERENCES


Table 1 Subtypes, prevalence and anatomical representation of lung cancer

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<th>Lung Cancer Subtypes</th>
<th>Clinical terms</th>
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<td>NSCLC</td>
<td>Adenocarcinoma</td>
<td>40%</td>
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<td>Squamous cell carcinoma</td>
<td>25-30%</td>
<td>Peripheral bronchi</td>
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<td>Large cell anaplastic</td>
<td>10%</td>
<td>Undifferentiated cells lacking features of small cell, squamous cell and glandular cell.</td>
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<td>SCLC</td>
<td>Limited and Extensive</td>
<td>10-15%</td>
<td>Confined to hemithorax, supraclavical lymph nodes or mediastinum</td>
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