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ORIGINAL ARTICLE

The Emerging Roles of Histology in the Management of Lung Cancer

NAIF ALSUHAYMI[1]
[1]*Department of Emergency Medical Services, Faculty of Health Sciences, AlQunfudah, Umm Al-Qura University, Makkah 21912, Saudi Arabia*
Correspondence to: Naif Alsuhaymi, Email: nasuhaymi@uqu.edu.sa

ABSTRACT

For many years, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) have been treated as single-disease entities. However, there are significant histologic and molecular differences between the various types of lung cancers. Such differences influence the various chemotherapeutic agents' outcomes and side effect profiles. For instance, bevacizumab causes significant pulmonary hemorrhage in squamous cell carcinoma; hence it is not recommended to treat such histologic subtypes. SCLC is more aggressive than NSCLC; therefore, it demonstrates differences in tumor behavior and the need to approach treatments differently. To date, studies of various lung cancers have provided new insight into their molecular characteristics. The histological classification does not only focus on the morphology but can provide detailed histological characteristics that will promote targeted therapy. Can this new knowledge assist in developing more effective drugs for lung cancers? In this paper, the review shows the advancements in histological diagnosis of lung cancers and their use in the optimal treatment of lung cancers.

Keywords: Small cell lung cancer, non-small cell lung cancer, histological subtypes.

INTRODUCTION

Lung cancer is the second most common malignancy by incidence but the topmost cause of cancer-related mortality globally (1). In 2020, 1.8 million people died of lung cancer, and there were 2.21 million new lung cancer diagnoses (1). The two primary basic histological classifications of lung cancers are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), which make up 80-85% and 10-15% of all lung cancers, respectively (2). There are further sub-classifications of these histologic subtypes based on WHO criteria. Sub-classification of NSCLC include adenocarcinoma, squamous cell carcinoma (SCC), large cell carcinoma, sarcomatoid carcinoma and adenosquamous carcinoma. Other sub-types are lung carcinoid tumors, lymphomas, adenoid cystic carcinomas, and sarcomas which are extremely rare (3).

For a long time, treatment for all NSCLCs has remained the same because it is treated as a single disease. Treatment has been based on the cancer stage with the use of platinum-based chemotherapeutic agents as the first line (4). There has been a significant advancement in the treatment of lung cancers due to an enhanced understanding of the pathogenesis of the cancers. Current treatment involves agents that target the molecular components of cancer; hence the new drugs target vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and insulin-like growth factor (ILGF). Clinical trials have demonstrated that there were different treatment outcomes for the various histologic types of lung cancer (5). Such a finding suggests that histology-based treatment should be embraced to ensure that there is optimal treatment of lung cancer in patients. Moreover, adopting an evidence-based practice in patient care requires advancement in treatment that is based on the histologic subtypes.

This article reviews the emerging roles that histology plays in the treatment of lung cancers. The author herein confirms that tremendous advancement has been seen regarding the histological diagnosis of lung cancers. This paper explores several research studies on the molecular basis of various histologic types of lung cancers and how such knowledge can benefit treatment through targeted therapy.

Histologic Characterizations of Lung Cancers: Lung cancers are traditionally categorized into two histologic subtypes. NSCLCs are malignant tumors of the lung that lack a small cell histologically (6). Small cell lung cancers (SCLCs), on the other hand, have small-cell components, as the name suggests. NSCLCs have heterogeneous histology, although the traditional subtypes are adenocarcinoma, large cell carcinoma, squamous cell carcinoma and adenosquamous carcinoma (7). The histological morphology is the standard for diagnosing lung cancers (8). However, there is an emerging trend of adopting the molecular basis of the tumors in their diagnosis.

NSCLC have a slower rate of aggression compared to SCLC. Its slow progression is the reason for late diagnosis of this type of cancer, often in advanced stages (9). Symptoms of NSCLCs tend to manifest late compared to those of SCLCs (9). The three major sub-classification of NSCLCs are based on the types of cells that predominantly exist in the tumors. Adenocarcinomas are the most prevalent types of NSCLC, which form 40% of all NSCLC cases (10). Moreover, of all types of lung cancers, adenocarcinomas are the most common, making up 30% of cases (10). NSCLC mainly occurs in the outer region of the lungs as well as the mucus-secreting glands. SCC accounts for 30% of NSCLC and often originates in the center of the lung (10). Smoking is linked to all types of lung cancers, although it mostly leads to SCC. The large cell undifferentiated NSCLC is the third most prevalent type and is noted to be more aggressive than the other subtypes. Large cell lung cancers account for 10-15% of all cases of NSCLCs and have been shown to originate from any part of the lungs (10).

SCLCs are highly aggressive neuroendocrine cancers that manifest rapid growth and early metastasis to distant tissues (11). Other notable characteristics of these cancers are high sensitivity to chemo-radiation as well as frequent association with other paraneoplastic disorders. These cancers originate from the peribronchial regions and invade the bronchial submucosal. It commonly spreads to the liver, adrenal glands, mediastinal lymph nodes, brain, and bones (12). SCLCs also secrete peptide hormones which result in the development of various paraneoplastic syndromes (13). There are also associated autoimmune processes that commonly accompany SCLCs leading to conditions like Eaton-lambert syndrome.

Recent studies have demonstrated unique molecular characteristics of the various histologic subtypes. For example, adenocarcinomas show glandular differentiation, which has resulted in categorization into bronchoalveolar carcinoma (BAC), papillary, acinar, and solid adenocarcinoma with mucin secretion (14). However, in most cases, there is a combination of the various subtypes of carcinoma, which have been shown to be thyroid transcription factor 1 (TTF1) positive. The BAC, on the other hand, is TTF1 negative but Cytokeratin 20 (CK20) positive. For most NSCLC, there is often significant downregulation of CD82, a phenomenon that leads to overexpression of epidermal growth factor receptor (EGFR) (Table 1).[16]

Table 1: Molecular markers associated with NSCLC subtypes

Histologic subtype	Immunohistochemistry marker	Molecular characteristics
Adenocarcinoma	TTF1- and CK20	P53 mutation, EGFR Kinase domain mutation
Large cell carcinoma	TTF1+,	Unknown
Squamous cell carcinoma	P63, CK6+, and TTF1-	p53 mutation

A study by Lazar et al. sought to characterize the molecular variations between adenocarcinoma and SCC using integrated genomic data. The various histologic subtypes of NSCLC portray different and varying molecular markers. The difference between SCC and adenocarcinoma can be made by analyzing the serine protease inhibitor Kazal type 1 SPINK1 and Bone morphogenetic protein 7 BMP7 biomarkers, which also act as potential drivers for carcinogenesis. For both subtypes of NSCLC, there is overexpression of the genes mitochondrial ribosomal small subunit genes (MRPS22), ring finger protein 7 (RNF7), and N-myc downstream regulated 1 (NDRG1) (17).

Genetic Modifications, Molecular characterizations, and Immunohistochemistry in Lung Tumorigenesis: Mutations of p53 which occur in most of the histologic subtypes of NSCLCs are depicted in Table 1. It confirms the significance of genetics in carcinogenesis. The molecular substances undergo alterations that culminate in the onset of the various histologic classifications of lung cancers (18). In SCC, there is a deletion of certain vital alleles that code for proteins that are essential in the maintenance of the anatomic integrity of the lung tissues. Deletion of the alleles is a product of various factors such as the lifestyle and genetic make-up of an individual (19). Metaplastic changes that may be seen in the early stages of the disease are the direct consequences of genetic alteration. p53 and RB transcriptional corepressor RB genes undergo mutations that are associated with the deletion of specific alleles (20). There is also genetic amplification on certain chromosomes, especially 3q26-3qter, which has phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (P13KCA) and p63 genes (21). Such amplification is a characteristic change in SCC development but non-existent in adenocarcinoma. Minute biochemical changes that accompany the various genetic alterations could be the reason for distinct histologic features of the spectrum of lung cancers (22).

EGFR, ILGF-1, and c-Met are important tyrosine kinase receptors that are also under tremendous alterations. At the intracellular level, the phosphatidylinositol 3-kinase causes transduction of the tyrosine kinases, a phenomenon that translates to either stimulatory or inhibitory effects on various cellular enzymes (23). Modification of ILGF-1 is associated with non-adenocarcinomas subtypes of NSCLCs such as SCC, which manifests significant downregulation of the insulin receptor substrate. The EGFR plays a pivotal role in adenocarcinoma development through mutations in KRAS proto-oncogene, GTPase KRAS (24). The KRAS mutation is marked by significant resistance to the effect of the growth factor receptor.

SCLCs demonstrate unique subtypes that are categorized based on the expression of either of the four transcription factors. Achaete-scute homologue 1 (ASCL1) transcription factor, also known as ASH1, is one of the common factors in SCLC. It dictates the lethal nature of these types of tumors. The second transcription factor is neurogenic differentiation factor 1 (NeuroD1) which is encoded in the human gene NEUROD1. This gene plays a significant role in controlling the expression of the insulin gene (25). Diabetes mellitus is a notable outcome of mutation in the insulin gene. The occurrence of the NeuroD1 transcription factor explains the reason for the association between SCLC and paraneoplastic syndromes. Yes-associated protein 1 (YAP1) transcription factor, on the other hand, regulates several genes that are crucial in carcinogenesis. These include Hoxa1, Birc2, and Amphiregulin (AREG) (26). YAP1 stimulates the Hippo pathway resulting in marked cell proliferation and tumorigenesis. Another important transcription factor in SCLC is POU class 2 homeobox 3 (POU2F3). Its main role involves the regulation of cell-type-specific differentiation pathways (27). Response to treatment of aggressive SCLC is greatly influenced by the effect of the pharmacologic agent on the various transcription factors described herein. Therapeutic research should therefore focus on these transcription factors to ensure that optimal treatment of SCLC is achieved.

Blood tumor markers in SCLC include neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), and progastrin-releasing peptide (ProGRP). The levels of these three tumor markers aid in the determination of histologic subtypes as well as in the differentiation between SCLC and NSCLC. According to Huang et al., ProGRP is more suitable for the diagnosis of SCC, whereas, for adenocarcinoma, it is recommended to combine both ProGRP and CEA (28).

Various gene mutations are the hallmark for the development of all the lung cancer subtypes. p53 mutations are the major molecular changes in carcinogenesis. For this reason, serum p53 plays a crucial role in the diagnosis and assessing the progression of lung cancers. Current research seeks to find out useful genes to suppress the various mutations which promote carcinogenesis. In a study by Qin et al., lncRNA F630028O10Rik is a tumor suppressor that has intriguing effects on the development of lung cancer (29). This tumor suppressor gene is also known as F63, and its main role is to regulate MiR-223-3p which inhibits angiogenesis in cancer development. lncRNA F630028O10Rik inhibits endothelial cells' clone formation as well as vascular endothelial growth factor A (VEGFA) (29). The F63 can therefore be a promising molecule that can be studied further and aid in the development of gene therapy in lung cancer treatment.

Introduction of New Treatments Based on Histological Characteristics: The various histologic subtypes of lung cancer have unique molecular characteristics that influence the behavior of the tumors as well as the response to treatment. NSCLCs have been well studied, and researchers slowly appreciate histology-driven pharmacotherapy in the management of lung cancers (30). Some of the latest advancements in treatment are considered below.

Gefitinib: This is a pharmacological agent that acts by inhibiting the kinase activity of EGFR mutations, thereby preventing proliferation that occurs as a result of endothelial growth factor receptor activation. Gefitinib also causes EGFR axon 19 deletions. Research has shown that histology plays a significant role in the treatment outcome of gefitinib (31-34). Individuals diagnosed with adenocarcinoma had a higher response rate (13-15%) compared to those with other histologic subtypes (4-6%) (32-34). The National Cancer Institute Clinical Trial of Gefitinib for treatment of stage 1B, II, and IIIA of NSCLC revealed significantly increased disease-free period and 5-year survival compared to placebo (35).

Pemetrexed: This is a multitargeted folate antimetabolite. Its brand names are Alimta, Taro-Pemetrexed, and Pemfexy. It is the approved first-line chemotherapy for non-squamous NSCLC. Various Phase III trials observed that participants with non-squamous NSCLC had better response rates with pemetrexed compared to those with other histologic subtypes (36-38). Such an observation has been explained by the presence of thymidylate synthase (TS) which is expressed in SCC (39). However, the mechanism by which the expression of TS influences response to pemetrexed is not yet well understood.

Bevacizumab: Bevacizumab is a monoclonal antibody with brand names Avastin, Zirabev, Bambevi, Mvasi, and bevacizumab-awwb. In one Phase III trial, combination therapy of bevacizumab with paclitaxel and carboplatin showed significantly improved efficacy (40-41). However, there was the observation of an increased risk of pulmonary hemorrhage among individuals being treated for SCC (42-43). Based on such findings, bevacizumab is cautiously used in squamous cell NSCLC (44).

DISCUSSION

The adoption of individualized and histology-driven treatment is an emerging trend in the management of both SCLC and NSCLC globally. In this regard, it is crucial to accurately determine the histologic subtype in each case (45). The poorly differentiated tumors may therefore make it hard for targeted treatment. For this reason, good sampling for biopsies should be encouraged to ensure that there are adequate cancerous tissue samples for pathologists to make an accurate histological diagnosis (46). While taking an example, a small section of undifferentiated tissues can be collected, leaving other lesions that could have provided a more

accurate histological picture. One way of overcoming such shortcomings in diagnoses is through effective tissue collecting skills that take into consideration adequate biopsies (47). Lack of adequate classification of lung cancer can predispose patients to unnecessary harmful and non-beneficial treatment. The case of pulmonary hemorrhage with treatment Bevacizumab treatment of squamous cell carcinoma is an excellent example of fatal adverse effects that occur when the histologic subtype is ignored when treating lung cancer.

Various histologic subtypes demonstrate unique molecular characteristics. Pathologists, therefore, need to preserve collected tissue for molecular analysis. Such practice enhances accuracy and promotes making specific diagnoses that aid in appropriate treatment. There is a need to identify possible mutations and use such information for targeted therapy. Gene therapy is an emerging treatment modality that takes into consideration the molecular basis of disease (48). It is thus sensible for pathologists to provide detailed information when reporting the biopsy results.

Most of the currently available data regarding the interaction between histological subtype and treatment outcome show that the approved pharmacological agents favor treatment of non-squamous lung cancer compared to SCC (49). Development of drugs focusing on single pathways such as EGFR or ILGF have proven to be ineffective. Some resistance to the chemotherapeutic agents has been noted. It should be borne in mind that such perceived resistance occurs because the various targeted growth factors may switch to other pathways (50). The new pathways like PDGF seem to be more common for the less differentiated cancers. Failure to investigate and understand all the possible pathways for the various histologic subtypes of lung cancer may bar optimal treatment of this disease in the population. Therefore, a more in-depth understanding of the molecular features of lung cancers is needed to succeed in developing targeted treatment with a lower side effect profile and better efficacy than what is currently in use.

In summary, new treatments of lung cancers that are highly tolerated by patients and have high efficacy require that clinicians take into consideration the specific histologic subtype. Effective and appropriate patient selection for particular chemotherapy should now be the norm rather than treating either SCLC or NSCLC as single disease entities. Current development in diagnostic techniques will therefore help promote the use of targeted therapy for lung cancers. The growing field of pharmacogenomics further encourages researchers and clinicians to adopt newer and targeted treatments for various diseases.

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