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An Overview of Non-Small Cell Lung Cancer and its Efficient clinical Management Technique

Mrs. Sumalatha Mani[1], Dr. Latha Parthiban[2]

Research Scholar, Periyar University, Salem, Tamil Nadu

Assistant Professor, Pondicherry University Community College, Kalapet, Puducherry[2]

Abstract: Lung cancer is one of the most frequently diagnosed cancers and is the leading cause of cancer-related deaths worldwide. The World Health Organization, on 9th December 2020, revealed lung cancer as one of the leading causes of death and disability between the years 2000 and 2019 all over the world. Among all the lung cancers, non-small cell lung cancer contributes for about 85% approximately. Only 15% of the lung cancer patients have the possibility of survival for about five years of maximum, after getting diagnosed. Initial diagnosis involves biopsy inspection followed by staging using computed tomography and positron emission tomography to detect the accurate therapy to be applied. Smoking has been proven to be the major cause for this disease however, non-smokers are also increasingly getting diagnosed in the recent years. Some common symptoms include cough, chest pain, fatigue, shortness of breath, weight loss, coughing up blood or mucous and loss of appetite. Surgical resection remains the most preferred option with comparatively high success rates. However, combination of therapies such as chemotherapy, radiation therapy etcetera could give good results. Identification of potential biomarkers could lead to an advantageous targeted therapy. This review discusses on the types, causes, risk factors, biomarkers, treatment methods and drug targets that have been reported earlier.

Keywords: Non-small cell lung cancer, adenocarcinoma, squamous cell carcinoma, biomarkers, targeted therapy.

I. INTRODUCTION

Primary lung cancer has become the number one killer and most common malignancies around the world **[1]**. The huge emergence of this lung cancer epidemic began in the 20th century. The prevalence of this disease in each country directly reflects the number of smokers present in that country [2]. Based on the smoking population, the highest and lowest incidence of lung cancer is observed. In China, the most populated country of the world, one- third of the world's smoking population is found which thereby has result in a very high prevalence of lung cancer in the past two decades. Contrastingly, in North America, a lot more non-smokers have been diagnosed with lung cancer **[3]**. Lung cancer is broadly categorized as small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) out of which NSCLC represents about 80-85% of all lung cancer cases [4]. Non-small cell lung cancer is a condition where cancer cells are formed in the lung tissues. These malignant cells are heterogenous in nature leading to different subgroups of NSCLC. Each of this subgroup has distinct group of cells which grow and spread in different ways. These subgroups are named based on the type of cells and their appearance in microscopic view

II. BACKGROUND STUDY ON LUNG CANCER

Lung cancer is divided into three forms, which are treated differently.

Lung Adenocarcinoma*:* Originates in mucous secreting glandular cells and gets spread to the alveoli. Lung adenocarcinoma is mostly found along the outer edges of the lungs and tends to have a slow growth progression when compared to other types of NSCLC. About 40% of all lung cancers is diagnosed as adenocarcinoma which is more often found in women and in non-smokers between the age of 20 and 46 **[4]**.

Squamous cell carcinoma: This type of non-small cell lung cancer begins in the thin, flat squamous cells which forms the inner lining of the lungs. Squamous cell carcinoma is the second most prevalent type of NSCLC, accounting for about 25-30% of all lung cancer cases. The development of this cancer type is usually slow but can eventually spread to other parts of the body. Squamous cell carcinoma often occurs due to smoking and affects the central part of the lungs [4].

Large cell carcinoma: In large cell carcinoma, the cells remain undifferentiated making themselves appear large and abnormal when viewed under microscope. This group of cells lack in the glandular or squamous differentiation [5]. LCC accounts for less than 10% of lung cancer cases. This type of cancer occurs peripherally and can affect any part of the lungs as its progression is very fast in growth and also spreads fast which makes it very difficult to treat [4]. It usually

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appears as sheets of large malignant cells and these cells are mostly associated with necrosis. LCC has some subtypes namely neuroendocrine LCC, basaloid LCC, lymphoepithelioma- like LCC, clear cell LCC and LCC with rhabdoid features. Theses subtypes are named based on certain distinct features present in them. Out of these subtypes, neuroendocrine LCC is the most fast- spreading, which contain features very similar to small cell lung cancer [5].

III. RISK FACTORS OF LUNG CANCER

***Genetic Susceptibility*:** Family history plays a major role in cancers. People who have an immediate blood relative with lung cancer are at high risk. Mutations in the tumor suppressor gene *TP53* is one of the major risk factors, which plays a vital part in the tumorigenesis of lung epithelial cells [6]. Polymorphisms in cytochrome *P450 1A1* (CYP1A1) and glutathione S-transferase M1 (GSTM1) contribute to a greater risk of lung cancer in females [7]. It is been reported that the susceptibility and severity of non-small cell lung cancer is increased by genetic polymorphisms in the promoter region of *TNF-α* [8]. People who have already been detected with lung cancer themselves are also at a high risk of developing a second tumor.

Tobacco Smoking: Smoking is proven to be the number one cause of lung cancer around the world. The smoking of cigarettes or pipes has been proven to be the most important risk factor for lung cancer. It is said that about 80-90% of the newly diagnosed people are current smokers [9]. Researches have also revealed that lung cancer will continue to be a leading killer unless a considerable reduction in the incidence of smoking occurs [10].

Passive smoking: Passive or secondhand smoking is the act of inhaling of smoke from other people's tobacco use. This condition leads to the occurrence of lung cancer even in non-smokers. About 1.6% of lung cancers are due to this reason [11]. It is also been reported that children who are exposed to passive smoking have a greater chance of getting affected by lung cancer as adults [12].

Radon: is an inert gas that is naturally formed in soil and rocks during the decay of Uranium-238. Studies reveal epidemiological evidences of radon causing lung cancer. Radon is considerable to be the second leading cause of lung cancer in the general population and it can even increase the risk in smokers [13].

Air Pollution: Long-term exposure to air polluted with various polycyclic aromatic hydrocarbon compounds, which are known as carcinogens and mutagens, are more likely to result in lung cancer [14]. Studies reveal that about 11% of lung cancer cases reported in Europe are due to urban air pollution [15].

IV. DIANOSIS OF LUNG CANCER:

Identification of potential biomarkers are helpful in efficient clinical management of NSCLC patients.

Epidermal Growth Factor Receptor (EGFR): The Epidermal Growth Factor Receptor is a gene located on chromosome 7 at the short arm in position 12. This gene encodes for a transmembrane glycoprotein of the protein kinase family **[20]**. *EGFR* being a cell surface protein, binds to the epidermal growth factor which induces dimerization of receptors leading to cell proliferation, metastasis and prevents apoptosis **[21]**. *EGFR* overexpression in about 62% of NSCLC **[22]**. Mutations in *EGFR* occur in exon 19 or 21 as in-frame or missense mutations respectively **[23]**. These mutations are most often found in female non-smokers who have been diagnosed with adenocarcinoma **[21]**. The detection of mutations in *EGFR* is done using gene sequencing methods and real-time polymerase chain reaction- based assays **[23]**.

Anaplastic Lymphoma Kinase (*ALK*)

The Anaplastic Lymphoma Kinase gene is found on the short arm of chromosome 2 at position 23. This gene codes for a tyrosine kinase receptor, which belongs to the insulin receptor superfamily **[24]**. Translocations or mutations in the *ALK* gene have been found in various types of cancer including non-small cell lung cancer. *ALK* is mostly rare, occurring in just 2- 7% of all types of NSCLC, but its prevalence is more common in patients who are rare or non-smokers. A few fusion partners of *ALK* such as *EML4*, *KIF5B* and *TFG* have also been found to occur in NSCLC **[25]**. The presence of *ALK* is detected using break-apart fluorescence in situ hybridisation (FISH) and reverse-transcription PCR (RT-PCR) **[24].**

Kirsten rat sarcoma viral oncogene homolog (*KRAS)*

RAS genes are oncogenes which were first discovered in a study of cancer- causing retroviruses in animals. *KRAS* is located on the long arm of chromosome 12 at position 12.1 **[26]**. This oncogene encodes for a GTPase superfamily protein. Mutation of this gene occurs due to a single amino acid substitution and this mutation is found in about 25-35% of NSCLC

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patients. Mutations are found in both former and current smokers and is more prevalent in Whites when compared to Asians **[26].**

MET proto-oncogene: The MET gene is found to be present on the long arm of chromosome 7 at position 31. This genes encodes a protein from the receptor tyrosine kinase family, which plays important roles in cell proliferation, survival, mortality and invasion[23]. Mutations occur as point mutations which are observed in about 4% of lung adenocarcinomas. NGS methodologies are used to detect these mutations[23].

Fibroblast growth factor receptor (FGFR):
FGFR gene is located on chromosome 8 at position 12. This gene encodes for a tyrosine kinase receptor from the *FGFR* family. The *FGFR* pathway is involved in enhancing cell survival, proliferation, motility and invasiveness. Mutations of this gene may occur due to gene amplifications, chromosomal and missense mutations **[27]**. These mutations have been detected in about 6% of squamous cell lung carcinomas. FISH and NGS methodologies are used to detect these mutations **[27]**.

B-RAF proto-oncogene, serine/threonine kinase (BRAF): *BRAF* oncogene is located on the long arm of chromosome 7 at position 34 which encodes for a serine/threonine kinase. This gene is involved in the RAS/RAF/MEK/ERK signaling pathway. When this gene is mutated, it promotes cell growth, proliferation and survival. *BRAF* mutations occur mostly in current or former smokers with adenocarcinomas [28].

***RET proto-oncogene*:** The RET encoding for a tyrosine kinase receptor is located on the long arm of chromosome 10 at position 11.2. It is involved in cell proliferation, differentiation, migration and neuronal navigation [29]. RET fusion are found approximately in 1-2% of NSCLC patients who are young non-smokers. FISH, RT-PCR and NGS methodologies are used in detecting the mutations and rearrangements in RET gene [30].

Neurotrophic receptor tyrosine kinase 1 (NTRK1): The NTRK1 proto-oncogene encodes for tropomyosin-related kinase A of the receptor tyrosine kinase superfamily. NTRK1 is located on chromosomes 1q21-22. This gene has a role to play in regulation of cell growth and differentiation. NTRK1 mutations are found in about 3% of adenocarcinomas. Some of the fusion partners include MPRIP and CD74 [31].

V. LUNG CANCER THERAPY

1. **Surgery:** Surgery remains to be the most preferred treatment method for non- small cell lung cancer at early stages. The aim is to remove the lung tumour completely along with some surrounding healthy lung tissues. Also, the nearby lymph nodes are removed to prevent the spread of cancer **[32]**. Several types of surgical methods are being implemented.
   a. **Lobectomy -** This is the most preferred surgical method for NSCLC. In this method, entire lobes of the lungs which contains the tumour is removed. Patients who had undergone lobectomy are observed to experience approximately 80%, 5- year cancer free survival **[33]**.
   b. **Pneumonectomy –** Pneumonectomy is preferred when the tumorous cells have occupied an entire lung. The entire lung is removed in this case particularly in cases where the tumour is closer to the chest centre. However, this method is mostly uncommon **[34]**.
   c. **Segmentectomy –** This method involves removal of a particular segment from a lobe when the patient's lung is detected of not being able to function properly with complete removal of a lobe. However, this remains to be a controversial method to follow since it has high local recurrence rates **[35]**.
   d. **Sleeve resection –** This method is implemented when the tumour is found to be present in the main airway (bronchus). The process involves cutting across the bronchus above and below the tumour and then re-joining the bronchi by reattaching the remaining lobes. This method is chosen in certain conditions to save parts of the lung **[36]**.
2. ***Radiation Therapy***: Radiation therapy is considered as an alternative for surgery in non- surgical candidates at stage I and II. This process involves usage of high energy x-rays to kill the tumorous cells and the therapy is continued for over a period of time. The disadvantage is that the beam of radiation also kills the healthy cells present in its path and therefore this therapy cannot be used against large areas of the body [37].
3. **Chemotherapy:** Chemotherapy is a treatment method in which powerful drugs are used to destroy the cancer cells and prevent them from growing and dividing. Chemotherapy is considered to be a standard treatment for adenocarcinoma and squamous cell carcinoma and has been proven to improve the quality of life at all stages of cancer [38]. A combination of 2 or 3 drugs is usually used in the therapy. Some commonly used drugs include Gemcitabine, Docetaxel, Vinorelbine, Paclitaxel and Carboplatin [39]. Chemotherapy also has the same disadvantage as in radiation therapy, causing damage to other healthy cells of the body.Also, side effects like nausea, vomiting, fatigue and loss of appetite are observed [38].

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4. Immunotherapy: Immunotherapy is a process designed to improve the body's natural immune mechanism to fight against cancer. The process involves usage of specially designed antibodies to block certain pathways like PD-1 which play important roles in cell growth and proliferation [40]. Before 1990, lung cancer immunotherapy focused on non-specific immune stimulants including *Corynebacterium parvum* which was used as an anti-tumour agent for NSCLC. This showed certain tumour- related responses but there was no improvement on the overall survival rate. Later, many new strategies have been developed [41]. Immunotherapy along with chemotherapy is a preferred treating method for people with advanced NSCLC

5. ***Targeted therapy :***Targeted therapy is a highly specific therapeutic approach, widely used to treat cancers. It involves usage of drugs which are specifically designed to identify and attack certain types of cancer cells. Targeted therapy is considered as the most promising treatment method for cancers resulting in improved survival rates. Identification of potential drug targets and biomarkers are important prerequisites for targeted therapy [42].

VI. CURRENT DRUG TARGETS FOR NSCLC

***EGFR* inhibitors:** *EGFR* mutations has been reported as a potential biomarker in NSCLC. Therefore, drugs that block the *EGFR* pathway may serve to be effective in preventing the growth of the cancer cells. These drugs are known as *EGFR* inhibitors. The most extensively studied *EGFR* inhibitors are Erlotinib and Gefitinib [43]. Both these drugs function by specifically inhibiting the intracellular phosphorylation of *EGFR* associated tyrosine kinase [42]. Erlotinib intake as pills has shown better results when compared to chemotherapy. Gefitinib is very common in Asia and some other parts of the world [43]. Osimertinib is another *EGFR* inhibitor, that inhibits both *EGFR-TKI* sensitizing and *EGFR T790M* resistance mutations [44]. Afatinib also works by a similar inhibiting mechanism which also inhibits *HER2* and *HER4* pathways along with *EGFR* and is one of the initial treatment options for NSCLC [45]. All the inhibitors mentioned here are taken in the form of pills which may have significant side effects such as acneiform eruptions, paronychia and xerosis [46].

***ALK* inhibitors:** In about 5% of people with NSCLC, the *ALK* genes appear to be mutated which results in quick growth of cancer cells **[47]**. Alectinib and Brigatinib are highly sensitive, orally bioavailable inhibitor, which inhibits the phosphorylation of *ALK* proteins resulting in decreased cell proliferation and tumour survival **[48]**. Ceritinib is also an *ALK* inhibitor in the form of an oral pill, which has shown an increased anti-tumour potency than Crizotinib, which is another inhibitor of *ALK* gene mutations **[49]**. Side effects of these inhibitors include nausea, vomiting, diarrhoea, constipation, fatigue, change in vision, inflammation in lungs and other parts, peripheral neuropathy and heart rhythm problems.

MET proto-oncogene inhibitor:In about 3-4% of NSCLCs, the MET exon 14 skipping is observed. Capmatinib is an approved MET inhibitor in combination with Gefitinib which is an *EGFR* inhibitor. Some commonly observed side effects include swelling in hands or feet, nausea or vomiting, loss of appetite and changes in certain blood tests [50].

RET inhibitors: RET fusions are found in about 1-2% of NSCLC. Selpercatinib is an approved drug inhibiting the mutations in RET genes with durable efficacy and reduced levels of toxic effects in both previously treated and untreated patients [52]. Side effects include dry mouth, high blood pressure, fatigue, swelling in hands or feet, skin rash, high blood sugar level, muscle or joint pain and low WBC, RBC or platelet counts.

NTRK inhibitors: NTRK fusions are found in various types of cancers. In adenocarcinomas, about 3% of NTRK fusions are found. Larotrectinib is an orally administered small molecule, which inhibits the NTRK fusion pathways. Larotrectinib is approved to be used in treating adult and paediatric patients with solid tumours in which NTRK gene fusions are observed [53]. Common side effects of using these drugs include dizziness, fatigue, weight gain, abnormal liver tests, hear problems and confusion.

VII. CONCLUSION

Lung cancer continues to be the leading cause of cancer-related deaths. Non-small cell lung cancer patients have approximately a five- year survival rate which is restricted only to about 15% of the diagnosed patients. The prevalence of this disease varies enormously between different parts of the world. One possible measure that could reduce the incidence of lung cancer will be to quit smoking. This can reduce the overall lung cancer cases in a huge amount. Identifying more potential biomarkers and drugs targeting the gene mutations can improve the condition.

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