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A REVIEW - PROGRESS IN THE TREATMENT OF NON SMALL CELL LUNG CANCER (NSCLC) IN A NEW ERA OF PERSONALISED MEDICINE

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ABSTRACT

Lung Cancer is the major cause of death all over the world. Statistically, China skilled substantial elevation in the rate of cigarette smokers since past twenty years and a pinnacle in lung carcinoma are further anticipated. Globally, Non-Small Cell Lung Cancer reports around 85% of cases of all pulmonary carcinomas. To ascertain the suitable treatment for Non-Small Cell Lung Cancer, exact staging with the help of computed tomography is very important. Practically, surgery would be the only reconcilable alternative for the cure. Although, 70-80% of the cases of lung cancers at the time of presentation itself develop metastases which are determined during the diagnosis. Personalized Medicine is the prominent practice of medicine that employs the patient's genetic profile for the prevention, diagnosis and treatment of the disease. Current proceedings in knowing the signaling pathways for cancerous cells and the affinity in these pathways, the significance of biomarkers and different receptors, and the interaction of various cancer promoting genes have assisted in progress of various targeted therapies enhancing the safety and efficacy. This boosts up the patient's attribute of life. The treatments are focused at genetic adjustments in cancerous cells. Several NSCLC subtypes are related to targetable biomarkers like alteration of Epidermal Growth Factor Receptor or EGFR, the existence of EML-4 and ALK fusion genes, ALK rearrangements or KRAS. The hostility to therapies is enhanced by the C-Met over expression or amplification. The purpose of this context is the treatment of Non Small Cell Lung Cancer (NSCLC) by the targeted therapies or personalized medicine.

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INTRODUCTION

Non Small Cell lung cancer is the most frequent type of lung cancer and is the leading global critical concern. It reports around 85% of all pulmonary carcinomas.^[1] China skilled substantial elevation in the rate of cigarette smokers since past twenty years and a pinnacle in lung carcinoma are further anticipated.^[2] Lungs are the set of cone shaped organs present in the thorax region of the body. These lungs conduct oxygen as a person breathes in, and as we breathe out, these lungs deliver carbon dioxide which is a waste product. The lungs have segments which are known as lobes. The left lung contains two lobes. The right lung is rather bigger than the left and it comprises of three lobes. Two subways open through the trachea or windpipe into these right and left lungs known as bronchi. Occasionally, these bronchi may also be involved in the cause of lung cancer. Minute air sacs called alveoli and very small tubes called bronchioles are the framework of these lungs. A very thin layer called pleura surrounds the outer wall of these two lungs and also lines the inner wall of the chest cavity. The pleural cavity contains pleural fluid which allows the lungs to move easily in the thoracic region when an individual breathes.^[3]

LUNG CANCER:

It is the unlimited growth of malignant or cancerous cells in the tissues of the lungs and divides rapidly to form a tumor. These tumors may also develop in the other parts of the lungs and may also spread to other vital organs of the body through systemic route.^[4]

This Lung Cancer is broadly categorized as

- (1) Small Cell Lung Cancer (SCLC) and
- (2) Non Small Cell Lung Cancer (NSCLC).

SMALL CELL LUNG CANCER (SCLC) also known as oat cell cancer is denoted by the small cells and they tend to grow rapidly in the tissues of the lungs to form a large tumor. It is usually associated with almost all smoking cases. Small Cell Lung Cancer (SCLC) accounts for lesser percentages around 13-14 % of deaths all over the world.^[5,6]

NON SMALL CELL LUNG CANCER: Non Small Cell Lung Cancer (NSCLC) accounts for higher rates of deaths worldwide i.e., around 85% of deaths. This is the most dangerous type of lung cancer which grows and spreads leisurely when compared to Small Cell Lung Cancer. This is broadly classified into four main subtypes based upon their size, chemical nature and shape when viewed under microscope.^[7] They are as follows.

Squamous Cell Carcinoma:

This is also known as epidermoid carcinoma and this accounts for about 25-30% of all NSCLC types. These types are frequently associated with the background of smoking and usually develop in the central portion of the lungs.

Adenocarcinoma:

This subtype of NSCLC accounts for around 40% of all lung cancer cases and is the most common of all subtypes. This adenocarcinoma may also be observed in the non- smokers. This is usually seen in females and in young people than in males.

Large-cell undifferentiated carcinoma:

This type of NSCLC is a very fast growing and is likely to form on the surface or outer edges of the lungs.^[8,20]

Bronchioalveolar carcinoma:

This is not so common type of NSCLC types and may be developed in the air sacs of the lungs.^[9]

RISK FACTORS OF NON-SMALL CELL LUNG CANCER:

There are various risk factors that cause this NSCLC. They are as follows.

- Smoking of Cigarettes or cigars and pipes.
- Passive or second hand smoking.
- Consumption of Alcohol.
- Due to exposure to radon.
- Family history of NSCLC.
- When treated with radiation therapy.
- Living in an area where there is air pollution.
- If infected by Human Immunodeficiency Virus (HIV)
- Exposure to some metals like asbestos, nickel, chromium, arsenic etc. ^[2]

SIGNS AND SYMPTOMS OF NON-SMALL CELL LUNG CANCER:

There may be no signs or symptoms observed at the initial stage of the disease but in the further stages the following symptoms may be seen. They are-

- Pain or discomfort in the chest.
- Inconvenience in breathing.
- Continuous cough which may go worse overtime.
- Unreasonable loss of weight.
- Fatigue.
- Difficulty in Swallowing.
- Sputum coming out with blood.
- Hoarseness.
- Appetite loss.
- The face of the individual gets swelled up.^[10]

DIAGNOSTIC TEST THAT DETECT NON SMALL CELL LUNG CANCER:

It is very essential to diagnose Non Small Cell Lung Cancer (NSCLC) for treatment before it reaches to the stage where it gets fatal. Diagnosis may include

- **Physical Exam and History:**
A physical examination of patient's body is taken to check the general signs of disease and history of is taken like patient's health, illness, whether the person is smoker or not and his past jobs etc.^[11]
- **Laboratory Tests:**
Medical tests of samples of blood, tissue, urine etc. are performed.
- **X-Ray of Chest:**
Picture of areas of chest is viewed when energy beam is passed through it to detect the presence of tumor.
- **CAT scan (Computed Axial Tomography):**
This is an approach of diagnosis in which depiction of regions of the body, like chest, is captured through imaging from various directions.
- **Cytology of Sputum:**
The smear of sputum which is coughed out from lungs is made and is observed under microscope.
- **FNA Biopsy of lungs:**
This is the Fine-Needle Aspiration of the lungs which is performed by using a thin needle to detect any superficial lumps or tumors.
- **Bronchoscopy:**
This is done by insertion of a thin tube- like instrument called bronchoscope into trachea and lungs through mouth or nose.
- **Immunohistochemistry:**
The use of antibodies to verify definite antigens in the sample of tissue.
- **Light and Electron Microscopy:**
The samples of cells and tissues are viewed under high power lenses of microscope for the confirmation of the type of lung cancer.^[12]

PERSONALISED MEDICINE:

Personalized Medicine is a novel medical treatment which is progressing more rapidly. This helps in the advancing of healthcare by giving a more accurate, foreseeable and considerable medicine that is tailored for the individual patient. This personalized medicine is emerging practice which requires the genetic profile of the patient for the prevention, diagnosis and treatment of the disease. This personalized medicine is initializing to revolutionize the treatment strategies. This strategy allows the healthcare providers to convey the prominence of treatment, anticipate liability to disease, enhance the recognition of disease and provide right drug to the right individual. The data of genetic information of an individual is taken from the Human Genome Project. The targeted biomarkers are enhancing the significance of this personalized medicine for prevention, diagnosis and treatment of the particular disease. These biomarkers include the DNA biomarkers, DNA tumor biomarkers and other general biomarkers. The prediction of the disease and the right treatment for it is based upon the genetic behavior of an individual.^[13]

The personalized medicine is getting more and more advanced by acquiring information from the genes of an individual and sequencing the genetic information which may help the healthcare providers to give the correct and precise treatment at right time. This personalized medicine has shown far better results in the treatment of cancers than any other disease.^[14] There is a great advancement in the treatment of Lung Cancer especially Non Small Cell Lung Cancer (NSCLC).^[15]

TREATMENT OF NON SMALL CELL LUNG CANCER (NSCLC) IN A NEW ERA OF PERSONALISED MEDICINE:

Non Small Cell Lung Cancer (NSCLC) is a very threatening type of lung cancer and must be treated at the initial stage itself for the better results. Few treatment options for NSCLC are Radiofrequency ablation (RFA), Chemotherapy (Chemo drugs such as Cisplatin, Carboplatin, Vinblastine, Etoposide etc. are used), Surgery (wedge resection or Segmentectomy, Pneumectomy, Lobectomy) Immunotherapy, Radiation therapy and various targeted therapies. Usually, more than one type of therapy is used for the treatment of Non Small Cell Lung Cancer (NSCLC).

PERSONALISED OR TARGETED THERAPY IN NON SMALL CELL LUNG CANCER:

There are more changes taking place in the cells of the lungs that is leading to the growth of large tumors, so researchers have found the advancement of these targeted agents to treat Non Small Cell Lung Cancer in a personalized way. These targeted therapies don't show many side effects when compared to other therapies.

Targeting of drugs on growth of tumor blood vessel:

In the human body, the growth of new capillaries or blood vessels for the tumors to sustain is known as Angiogenesis. Few angiogenesis inhibitors do not allow the nourishment of these tumors and prevent their growth.

Ramucirumab and Bevacizumab are the two angiogenesis inhibitors and the two monoclonal antibodies which are used in the treatment of non small cell lung cancer. These are the drugs that may help to target the specific receptor for Vascular Endothelial Growth Factor (VEGF). Bevacizumab, which is commonly known by the name- Avastin, is usually given at the time of chemotherapy and if the cancer shows positive results to this drug, chemotherapy must be discontinued and then only this drug must be given till the cancer develops once again. Whereas, Ramucirumab is usually combined with the chemotherapy and given.^[16, 20]

EGFR targeted drugs:

The resistance towards different therapies is shown by the Epidermal Growth Factor Receptor (EGFR) and various other biomarkers. This EGFR is present in more amounts in the cells of Non Small Cell Lung Cancer (NSCLC) patient and may also lead to mutation in the genes of EGFR. This EGFR helps in the rapid division of the cancerous cells in the lungs. The drugs which are helpful in targeting EGFR are Gefitinib, Erlotinib, Afatinib etc. These drugs prevent the mutations in EGFR and also halt the growth of the cells of lung.

Erlotinib is the drug that is used if chemotherapy doesn't show any response in the advanced NSCLC apart from the mutations of EGFR.^[17]

Drugs targeting ALK-gene:

There are rearrangements in the genes in most of the cases and these are usually shown up by the ALK rearrangements. Most of the Adenocarcinoma cases which are a subtype of Non Small Cell Lung Cancer (NSCLC) show these kinds of rearrangements. The growth of abnormal ALK protein is observed in the ALK gene rearrangement that tends the unusual growth of cells. The drugs which target the ALK gene are: Ceritinib and Crizotinib.

The individual having ALK gene mutation, these targeted drugs may hamper the unusual ALK gene and may stop the tumor growth by shrinkage. These drugs may also help when the chemotherapy of the patient is stopped. These drugs may also cause few side effects like nausea, constipation, change in vision etc. Few other side effects may be fatal such as damage in the liver, inflammation in the lungs, change in the rhythms of the heart etc.

Also other targeted therapies such as C-Met over expression helps in the confrontation to various other therapies and the existence of EML-4 (Echinoderm microtubule-associated protein like 4) and ALK (Anaplastic Lymphoma Kinase) gene combination may show better results to the therapy.^[18]

There is a rapid growth of these targeted agents and the biomarkers for the prevention of the Non Small Cell Lung Cancer (NSCLC) and thus the rate of cure are also increasing in the personalized medicine. Combination of all these biomarkers and targeted agents and sequencing them correctly in an individual along with the other therapies may show a greater advancement in the new era of personalized medicine. According to previous study, many more clinical trials are performed to prevent the growth and metastasis of Non Small Cell Lung Cancer (NSCLC).

Other therapies such as Immunotherapy for Non Small Cell Lung Cancer (NSCLC) may be of a greater advantage. This may help in boosting up of patient's attribute of life.^[19]

CONCLUSION

Attempts have been made to prevent the growth of Non Small Cell Lung Cancer (NSCLC) in a new era of personalized medicine. This is achieved by combining various targeted agents or biomarkers and sequencing them properly. The drugs may be combined with the other alternative therapy to get better results and the overall survival of the patient may be seen. The use of these biomarkers showing accurate results based upon the personalized behavior of the individual may become a future of medicine in treating not only advanced metastatic Non Small Cell Lung Cancer(NSCLC) but also various other cancers too. The future approaches to personalized medicine in treatment of various diseases may be remarkable. Although considerable efforts are being made for the treatment of metastatic Non Small Cell Lung Cancer (NSCLC), the knowledge of combination of various other therapies with targeted agents or biomarkers is essential.

CONFLICT OF INTEREST:

Authors state that there is no conflict of interest.

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ABBREVIATIONS:

SCLC-Small Cell Lung Cancer

NSCLC - Non Small Cell Lung Cancer.

CAT- Computed Axial Tomography.

RFA -Radiofrequency ablation.

DNA-Deoxyribonucleic acid.

VEGF-Vascular Endothelial Growth Factor.

EGFR-Epidermal Growth Factor Receptor.

ALK- Anaplastic Lymphoma Kinase.

EML-4- Echinoderm microtubule-associated protein like 4.

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