Indo Global Journal of Pharmaceutical Sciences, 2022; 12: 82-91

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Lung Cancer: How Well We Have Fared?

Pradeep S. Patil *, Hitendra S. Mahajan

R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dhule (Maharashtra) 425405, India.

Address for Correspondence: Pradeep S. Patil, patilpradeep19@yahoo.com

Received: 26.02.2020
Accepted: 08.09.2021
Published: 31.01.2022
Keywords
Adenocarcinoma, Chemotherapy, EGFR, Lung cancer, Driver mutations.

ABSTRACT: Lung Cancer has been one of the most common causes of death worldwide. With the death toll increasing in millions every year globally it has become a global scourge. With poor prognosis and disappointing 5 years survival rate post diagnosis, treatment for this disease has been ambiguous. Various advances in treatment are being made but till date the 5 years survival for major patients remains a dream. This review encompasses different treatment options that are available, problems associated with treatment and future perspective for the treatment of lung cancer.

Cite this article as: Patil, P.S.; Mahajan, H.S. Lung cancer: how well we have fared? Indo Global J. Pharm. Sci., 2022; 12: 82-91. **DOI**: http://doi.org/10.35652/IGJPS.2022.12007 .

INTRODUCTION

Lung cancer is one of the most fatal diseases of the modern era. It is characterized by cell proliferation, resistance to cell death, tissue infiltration, and development of blood supply channels to the tumor, metastasis, and organ dys-functioning [1]. Instability in the genome is usually responsible for causing spontaneous rise in inflammatory processes. This genetic mutation within the cell causes cancer [2]. According to WHO nearly 8.8 million deaths have been reported due to cancer in the year 2015, which makes it the second largest cause of death worldwide. Smoking has been the leading cause of deaths and is accountable for almost 22 % of cancer deaths worldwide and cases in India are on rise as a result of smoking. [3]. The following review intends to throw light on the various treatment options available at hand, the problems associated with these treatment options and how the new treatment options can prove to be a boon for treatment of this disease.

Epidemiology of lung cancer

Lung cancer has been the leading cause of deaths related to cancer over past three decades. It is more frequent in males as compared to females. It is the second most common cancer in men and women. India reports about 10% of the world lung cancer incidents. According to GLOBOCAN 2018 reports the estimated incidences of lung cancer in India was 67,795 in all ages and sexes, the incidence rate per 1, 00,000 was 6.52. The age standardized rate per 1, 00,000 Was 5.4 and cumulative risk was 0.65 globally. There were 48,698 new cases reported in males and, also the incidences of lung cancer in women are increasing at alarming rate. The overall lung cancer related mortality in India was estimated to be 63,475 in 2018 making it one of the prevalent causes of cancer related deaths [4]. **Figure 1** illustrates the various types of cancer and their occurrences [5].

CLASSIFICATION OF LUNG CANCER

Histologically lung cancer can be categorized as Small Cell Lung Cancer and Non-Small Cell Lung Cancer. Small Cell Lung Cancer accounts for 20% of total lung carcinomas and Non-Small Cell Lung Cancer accounts for 80% of total lung carcinomas. Non-Small Cell Carcinoma is further classified as Squamous Cell Carcinoma, Adenocarcinoma and Large Cell Carcinoma [6].

Small Cell Lung Cancer (SCLC)

The term small cell lung cancer was first coined in 1926 [7], also referred as oat cell carcinoma. Small cell lung cancer is characterized by formation of malignant (cancer) cells in the tissues of the lung. Signs and symptoms of small cell lung cancer include coughing, shortness of breath, and chest pain. It is usually associated with areas of larger airways and is characterized by rapid growth and large size. More than 90% patients have been heavy smokers or are currently heavy smokers and are elderly. SCLC is defined as “a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli” [8]. Prognosis for this

cancer is worse with median survival time without treatment reported is of 2-4 months [9]. With minimum treatment options available and poor prognosis SCLC treatment has been disappointing.

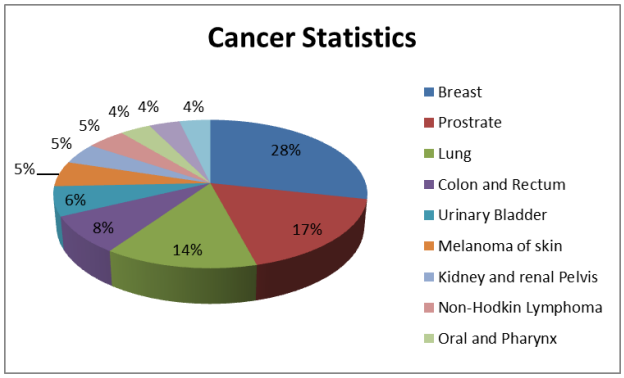

Fig. 1. Cancer Statistics

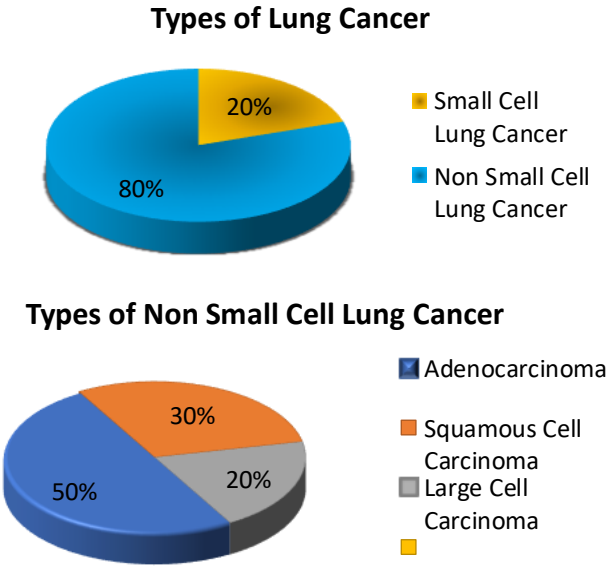

Fig. 2. Classification of lung cancer

Non-Small Cell Lung Cancer

There are three main subtypes of NSCLC.

- **Squamous Cell Carcinoma [10]** It accounts for nearly 30% of all NSCLC**.** It originates near central bronchus. It is characterized by a hollow cavity and tissue necrosis at the center of the tumor. Development of this type of cancer cells is slow when compared with other type of lung cancers.
- **Adenocarcinoma** It accounts for nearly 40% of all NSCLC [11]. It usually originates in the peripheral lung tissue [12]. Most common cause of this type of lung cancer is smoking, however cases of non- smokers or never smokers have also been reported [13]**.**
- **Large Cell Carcinoma** It accounts for nearly 20 % of all NSCLC. It develops very quickly and initiates its development in any part of the lung.

Figure 2 illustrates the detailed classification of lung cancer and their Subtypes

CAUSES OF LUNG CANCER

➢ **Smoking**

It has been the major contributor among the causes of lung cancer. With the increase in cigarette smoking over past few decades the incidences of lung cancer reported have increased drastically [14]. Smoking is known to cause almost 80% of lung cancer deaths globally [15].

➢ **Passive Smoking**

Passive smokers are those people who have never smoked in their lifetime but are living or working with a smoker [16]. Such people are at risk of inhaling the tobacco smoke and may account for approximately 10% of total lung cancer cases [17].

➢ **Occupational and environmental exposure**

Asbestos, radon, chromium, nickel etc., have also been found to cause lung cancer.

Table 1 gives a detailed account of causes of lung cancer.

History of lung cancer Figure 3 gives a brief idea about the history of detection of lung cancer [22,23].

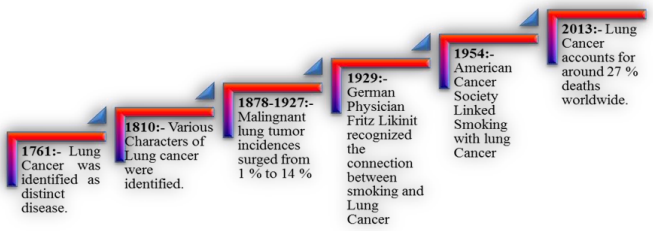

Fig. 3. History of lung cancer

Stages of lung cancer

Non- Small Cell Lung cancer can be categorized under 5 stages viz stage 0 to Stage IV. Each stage is further subdivided into different substages. **Table 2** gives a brief idea about different stages and their treatment options. **Figure 4** gives a brief idea of different stages of lung cancer.

LUNG CANCER TREATMENT OPTIONS

The various treatment options for lung cancer have been described in detail in the following section.

Surgery

This option is preferred with patients having stage I, II and IIIA NSCLC if the tumor can be resectable and pain is bearable [14].

- **Wedge resection**

In this type of surgery, a small portion of healthy tissue of lung surrounding the tumor is removed along-with the tumor. It is usually performed for small peripheral tumors and do not lie within segmental boundaries. Limitation of such a type surgery includes chances of recurrence of tumor and possibly lesser resection [24].

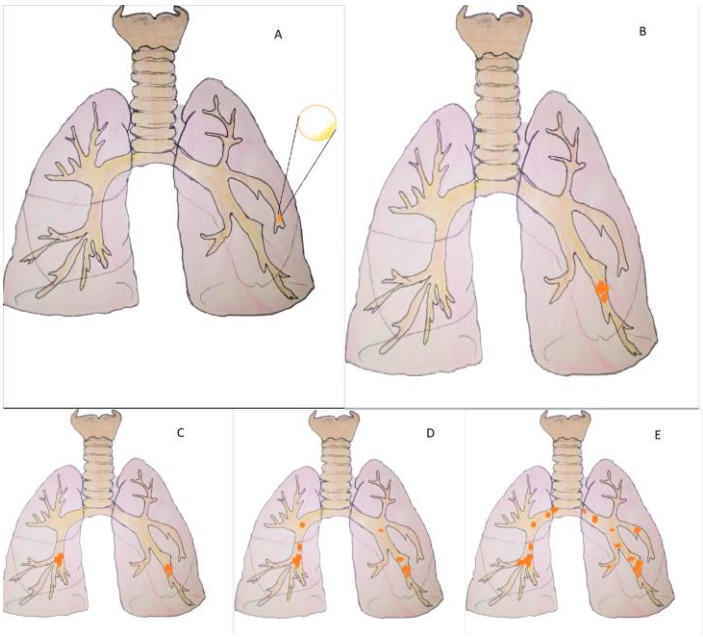

Fig. 4. Stages of lung cancer. A) Stage 0 (Carcinoma In-Situ), B) Stage I, C) Stage II, D) Stage III (Metastasis) and E) Stage IV.

- **Lobectomy**

In this type of surgical procedure, a part of lobe is removed. This type of procedure involves notable peril where patients might experience post-surgery complications such as atrial arrhythmia and even respiratory failure in certain cases [25].

- **Video Assisted Thorascopic Surgery (VATS)**

Currently many surgeons worldwide prefer this surgical procedure. This approach typically involves a 5-8 cm incision and 2-4 port sites [26]. A thorascope is introduced through the access incision site and removal of the lobe can be carried out with it. This procedure offers an advantage over open lobectomy of avoiding the need of larger incisions for surgery [27]. Limitations of this type of surgery include failure to maintain single lung ventilation, dense pleural symphasis, tumors lying in central region and larger tumor than those in case of incision.

Robotic Lobectomy

With amelioration in surgical procedures Robotic Lobectomy has offered many merits which include lesser pain at the port site as compared to VATS, binocular vision permitting precise dissection and elimination of the necessity of access incision [28].

Table 1: Causes of lung cancer

Sr. No	Causes of Lung Cancer	Mechanism by which cancer is caused	Reference
1	Smoking (Smokers and Non-smokers)	Cancer causing agents are metabolic products of tobacco which are metabolized by Cytochrome P-450 enzyme, examples include PAH – benzopyrenes and nicotine derived nitrosamine ketone (NNK or NNAL) which when react with DNA form DNA adducts. Conversion of the methyl adducts from former to 7-methylguanine or o6-methylguanine by alpha – hydroxylase may cause miscoding and results in permanent mutation; this causes oncogenic activation or suppression of genes responsible for tumor suppression. Chances of people acquiring lung cancer are 20% which increases with the intensity of tobacco consumption. Other carcinogens present in tobacco smoke include Acrolein, cadmium, chromium, nickel, arsenic, radioactive polonium (Po210), butadiene,	[18]
2	Radon	Considered as the second most common cause of lung cancer Radon-222 is a radioactive gas released from natural decay of uranium. During spontaneous decaying other radioactive atoms (radon progeny) release substantially harmful radioactive particles, which when inhaled in excess may lead to damage to the cells lining the lungs by damaging the DNA. This is responsible for lung cancer in later stages.	[19]
3	Asbestos	With inhalation of asbestos for many years the likelihood of acquiring lung cancer increases as inhalation of asbestos, microscopic fibers of toxic minerals are loaded in lung tissue which may cause genetic mutations and damage at the cellular level, thus leading to lung cancer. Synergistic interactions are also expected with asbestos and tobacco smoke.	[20]
4	Chromium, Nickel etc.	Exposure to heavy metals may be one of the factors responsible for lung cancer as heavy metals generate free radicals and interfere with many cellular reactions.	[21]

Table 2 Stages of lung cancer and their treatment options [5].

Sr. No	Description	Treatment Option	Prognosis
01	**Stage 0** [5, 38] Diagnosis at this stage is fairly infrequent but might be possible with CT scanning. Also known as Carcinoma In-situ. In this stage the cancer is confined to inner layers and hasn't spread to surrounding tissue. These tumors are very small and sputum cytology can be a promising tool to diagnose such tumors. As they do not invade in surrounding area they are frequently termed as non-invasive. They rarely show symptoms	Surgery	Curable with treatment.
02	**Stage I** From this stage tumors are termed as invasive. The tumor is still confined to the layers of cell and has not invaded in the surrounding tissue, but it has spread beyond the top layers of the cell lining the airways. Around 15 % patients are diagnosed at this stage. Depending on their size they are further classified as Stage IA and Stage Ib. In Stage I A the size of tumor is less than 3 cm in diameter. In Stage I B the size of tumor is more than 3 cm in diameter.	Surgery in most cases [39]. Stereotactic body radiotherapy (in cases when patient is inoperable) Chemotherapy or adjuvant therapy (usually for stage I B lung cancer showing aggressive nature)	Fairly good [40], roughly 50 % patients are alive after 5 years after diagnosis.
03	Stage II [41] Referred as localized cancer. These tumors have spread to nearby lymph nodes and to areas of the airway or lining of lungs. They are further classified as stage II A and Stage II B lung cancer. In Stage II A the size of tumor is about 3-7 cm in diameter and shows invasions to nearby lymph nodes. In Stage II B the tumor is usually between 5-7 cm or greater and have invaded surrounding lymph nodes.	Surgery and Adjuvant Chemotherapy.	5year survival rate is around 30 % in this stage.
04	**Stage III** [42-47] Classified as Stage III A lung cancer (Early Stage) and Stage III B lung cancer (Advanced Stage). Stage III A lung cancer: In this stage the tumor has spread to nearby and distinct lymph nodes. This stage is usually referred as locally advanced stage of lung cancer. Stage III B lung cancer: In this stage the tumor has spread to distinct lymph nodes and to surrounding organs such as heart or esophagus. The tumor can vary in size.	Stage III A Chemotherapy and radiation therapy. Such therapy is curative. Stage III B Chemotherapy and radiation therapy. In some cases, Surgery might be possible once the size of tumor is reduced.	5-year Survival rate for Stage III A is roughly 20 % and for stage III B is merely 5 %.
05	**Stage IV** [48] Most advanced stage of NSCLC. Around 40 % patients are diagnosed at this time. In this case the tumor has become malignant and has shown metastasis. The spread of tumor is not limited to lung or surrounding organs.	Incurable. Attempts are made to extend survival time and reduce symptoms. Treatment options include Chemotherapy, Targeted therapy, and Immunotherapy	5-year Survival rate is merely 1-2 %

Radiotherapy

This treatment option is preferred in locally advanced and archaic stages of NSCLC [29].

- **Stereotactic ablative radiotherapy (SABR)**

This is perhaps the most advanced radiotherapy technique for inoperable patients having peripheral early stage NSCLC [30]. SABR employs fine beam of radiations exceeding 100 Gray, which are targeted at tumor via different angles. Tumor draws high dose of radiation and lesser dose is received by normal cells thus causing minimal damage to the normal cells [31]. The treatment sessions are divided over few weeks [32].

- **Conventional radiotherapy** [5]

Radiotherapy technique involves delivery of high intensity beam of X rays to treat lung cancer. There are two types of radiotherapy a) external beam radiation therapy and b) brachytherapy (internal bean radiation therapy).

- **Other techniques of radiotherapy**

These can involve three-dimensional conformal radiation therapy (3D-CRT), Intensity modulated radiation therapy (IMRT) and Stereotactic radiosurgery (SRS).

Chemotherapy

Chemotherapy is usually used along-with other treatment options like surgery and radiation therapy. The use of Chemotherapy depends on the stage of lung cancer. The various conditions under which chemotherapy can be used are as follows:

Before Surgery It may be used along-with radiation therapy to wane the size of a tumor (neo-adjuvant therapy).

1. **After Surgery** It may be used along-with radiation therapy where it anchors the role of destroying traces of cancer cells (adjuvant therapy).
2. As a concurrent therapy, where chemotherapy in combination with radiation therapy helps to destroy cancer cells which are inaccessible to surgical procedure owing to their growth in nearby vital structures of organs.
3. Chemotherapy is used as a main treatment option in advanced cancer stages or in cases where patients are inoperable.

Chemotherapy usually is a combination of two drugs. Adding one more drug shows negligible effect in the treatment; Moreover, it causes more harm than good as it adds to the side effects. Chemotherapy is carried out in cycles which last for one to three days followed by a resting period. Chemotherapy cycles are carried out for over 3-4 weeks. The first reference to chemotherapy dates to 1948 when journal Cancer published a paper authored by David Karnofsky entitled "The use of nitrogen mustards in the palliative treatment of carcinoma" (with particular reference to bronchogenic carcinoma) [33]. With this initial breakthrough it was expected that new findings in the era of chemotherapy would become the biggest milestone in treatment of cancer, but in the next 4 decades apart from few drugs like cyclophosphamide, methotrexate, vincristine, and doxorubicin, which were the first-generation drugs paved their way as chemotherapeutic agents. These drugs were widely used in 1970-80s in the treatment of SCLC, though they proved to be ineffective in NSCLC. Few drugs like cisplatin, ifosfamide, mitomycin-c, vindesine, vinblastine and etoposide showed positive results with NSCLC. The response time was limited to an average of 2-3 months and median survival of 6-8 months [34]. Greater response rates were reported with combination chemotherapy cisplatin which was considered as most active drug and found to be one of the chemotherapeutic agents in combinational therapy [35, 36].

A brief history of various chemotherapeutic agents is given in **figure 5**.

Drug Targeting: Chemotherapy was considered as a boon for prolonging survival of patients for many decades despite shortcomings. Extensive research and clinical trials are being carried out to identify different targets for delivery of drug to lung cancers. Peculiarity of such targets can be ascertained by oncogene dependency, DNA damage response, angiogenesis and cellular plasticity. An ideal target is the one that leads to expulsion of carcinoma cells with a greater therapeutic efficacy. Target therapies include drugs targeting to driver mutations, those inhibiting immune checkpoint molecules and targeting speculated vital molecules in cancer cell proliferation and survival. Till date various driver mutations have been explored and targeting such mutations has paved the way for more efficient and site-specific drug delivery with minimum damage to surrounding tissue. **Figure 6 and 7** gives a brief idea about different driver mutations and their frequencies.

Since, driver mutations are usually distinct and it is evident that each patient will have one of these driver mutations, and if a drug specifically targeting that mutation is administered an evident pharmacological response can be obtained. Various researches and clinical trials have come up with different drugs that target particular driver mutation.

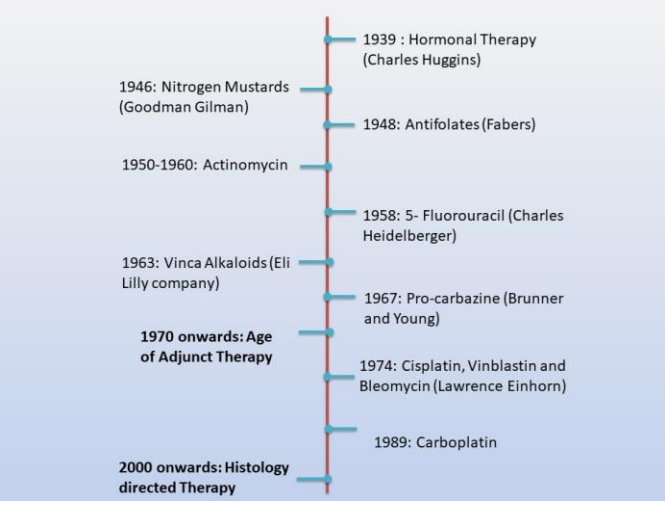

Fig.5. History of cancer chemotherapy [37].

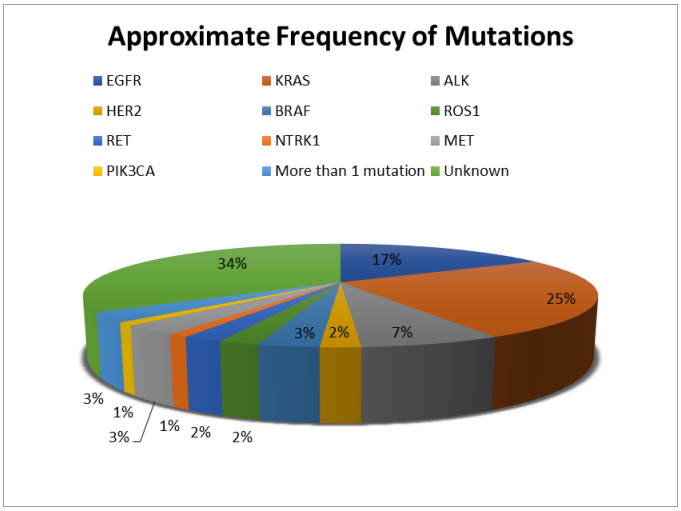

Fig. 6. Approximate frequency of mutations reported in adenocarcinoma.

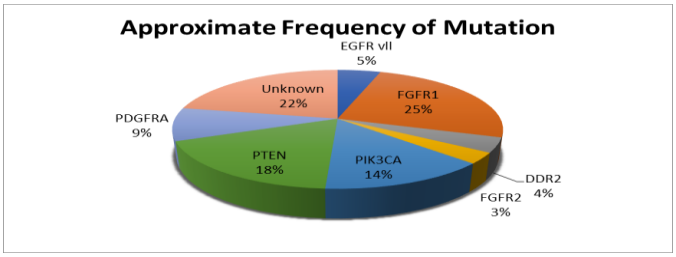

Fig. 7. Approximate frequencies of mutations reported in squamous cell carcinoma.

DRIVER MUTATIONS AND DRUG TARGETING IN LUNG ADENOCARCINOMA

In this section various driver mutations have been discussed along with the current status of drugs that are used for targeting. The different driver mutations are as follows:

- **EGFR**

Epidermal Growth Factor receptor, a member of family tyrosine Kinase receptor is a transmembrane glycoprotein localized at p12 cytoband of chromosome 7. Dimerization due to binding of ligand leads to activation of protein kinase thus initiating downstream signaling pathways [49]. It is overexpressed in lung neoplasia as compared to normal tissue at the vicinity [50]. Most Common Mutation observed is on exon 18-21 which are displayed by point mutations at position 858 from Leucine to Arginine and deletion (de1E746-A750) within exon 21 and exon 19, respectively [51, 52]. This overexpression makes it an exclusive target for drug discovery. It is involved in varied functioning of tumor cell specifically cell proliferation, Apoptosis, Angiogenesis and Metastasis.

Resistance: Resistance to tyrosine kinase inhibitors occurs due to EGFR mutation T790M in exon 20 of TK domain [53]. It is anticipated that substitution of Methionine rather than Threonine at 790 positions within ATP binding packets of TK domain results in conformational changes causing loss of binding site for drug [54]. Resistance to third generation EGFRTKI (e.g. osimertinib) occurs by EGFR Cys 797 Ser mutation [55].

Drugs used and their status [56,57]
Approved: Erlotinib, geftinib, afatinib, osimertinib and olmutinib.
In Clinical Trials ASP8273 (Phase III), EGF 816 (Phase II), PF-06747775 (Phase II). Drugs can be given as monotherapy or can be combined with chemotherapy.

- **KRAS**

Kirsten Rat Sarcoma viral Homolog is the most common driver alteration in lung Neoplasia, usually found in 25% patients with adenocarcinoma [58]. It is a G-Protein encoding proto-oncogene predominantly linked with RAF/ MAPK/MEK/ERK signaling cascade. Hydrolyzation of RAS bound GTP to GDP results in simultaneous activation of downstream signaling pathways. Substitution of single amino acid usually at codon 12, 13 and 61 with exon 2 and 3 is most common mutation [59].

Drugs used [56,57]: Combination of Selumetinib (oral MEK inhibitor) and docetaxel (Phase III) have shown promising results, Trametinib is in Phase III.

- **ALK Translocation**

Anaplastic Lymphoma Kinase gene showed activation by translocation in about 3-5% patients [60, 61]. Fusion in opposite direction of intracellular domain of ALK with N-terminus of Echinoderm. Microtubule –associated protein like 4 genes (EML4) owing to short inversion of P arm of Chromosome 2 causes fundamental TK activity and activation of PI3K –AKT and MAPK signaling pathways. This results in proliferation of cell and inhibition of apoptosis.

Resistance occurs due to secondary mutation and 1151Tins, Leu1152 Arg, Cys 1156Tyr, Ile1171Thr, Phe1174Leu, Val1180Leu, Leu1196Met, Gly202Arg, Ser1206 Tyr, and Gly 1296 Ala mutations [62].

Drugs used [56, 57]
Approved Crizotinib (c-met inhibitor), Ceritinib, Alectinib, Brigatinib and Loratinib.
In Clinical Trials X-396 (Phase III), Enterectinib (Phase II), TSR 011 (Phase II).

- **BRAF**

A vital downstream signaling molecule of KRAS which activates MAPK Pathway. It is observed in 3-5% patients with adenocarcinoma. It is a serine / threonine protein kinase, which is activated on phosphorylation in a GTP dependent manner interceding essential cellular functions including survival and proliferation [63]. Mutations usually occur in exon 15 and exon 11 [64].
Drugs used [56, 57]
Approved Cetuximab
In Clinical Trials Vemurafenib (Phase II), Dabrafenib (Phase II), Dabrafenib + Trametinib (Phase II).

- **ROS1 Translocations**

Rearrangement of Chromosomes involving ROS1 gene on 6q22 has been reported in 1-2 % patients with adenocarcinoma [65].
Drugs used [57]
Approved crizotinib
In Clinical Trials ceritinib, cabozantinib, enterectinib, loraltinib (Phase II).

- **MET**

MET proto oncogene on chromosome 7q31, encodes protein hepatocyte growth factor receptor (HGFR) having TK activity. Activation occurs due to reduced degradation, mutation or over-expression causing cell to become malignant [66,67], anticipated mechanism of activation is by amplification on exon 14 splice mutation of the MET receptor gene.

Drugs used
In Clinical Trials [56, 57] Onartuzunab and Gefitinib/ Erlotinib, Crizotinib, Carbozantinib, INC280 (Phase II).

- **HER2**

A receptor of TK from EGRF/ERBB family undergoes hetero-dimerization with any of family members resulting in auto-phosphorylation of Tyrosine residue and initiates diverse downstream signaling pathway.

Resistance Due to Insertion in exon 20 of TK domain [68].
Drugs used [56, 57]
In Clinical Trials Trastuzumab, Afatinib, Dacomitinib (Phase II).

- **RET**

Found in 1-2 % patients comprising of never smokers and younger patients with adenocarcinoma [69,70].

Drugs used [56,57]
In Clinical Trials Vandetinib, sunitinib, sorafenib, carbozantinib, alectinib, apatinib, lenvatinib, ponatinib, combination of vandetanib and everolimus (Phase II).

- **PI3KCA**

Such mutation is found in 1-2% patients. Cases reported show deregulation of Phosphatidylinositol-3 kinase (PI3K) pathway due to alterations in PIK3CA gene which is central to the cascade [71].
Drugs used [56, 57]
In Clinical Trials LY3023414 (Phase II), PQR309 (Phase I).

- **NTRK1 Translocation**

It is a rare driver mutation in patients with NSCLC [72].
Drugs in Clinical Trials [56, 57] entrectinib and cabozantinib (Phase II).

DRIVER MUTATIONS AND THEIR TARGETING IN SQUAMOUS CELL CARCINOMA

Various driver mutations are present in squamous cell carcinoma. The following section highlights the different driver mutations and the therapeutic regime used.

- 10-25% of patients having squamous cell carcinoma have shown gene amplification of FGFR1. Probable therapeutic regime includes Pan FGFR inhibitors [73].
- 4% of patients with squamous cell carcinoma have reported DDR2 gene encoding. Drug of choice is dasatinib [74].
- Recent study demonstrated co-amplification of PRKC1 and SOX2 in squamous cell carcinoma. Efforts are being carried out to identify other driver mutations in squamous cell carcinoma [75].

METABOLISM PROCESS IN CANCER: TUMOR MICRO-ENVIRONMENT

Normal cell and cancer cell Normal cells usually follow normal metabolic functioning and replicate via mitosis process. At a certain point due to a process called as contact inhibition, the growth is stopped, and cells do not divide further. During this process if certain cell is mutated, it gets terminated due to apoptosis [76].

Cancerous cells on the contrary do not follow normal metabolic functioning and during replication if a cell gets mutated due to alterations in DNA it becomes defiant to apoptosis process, thus surviving and replicating at a faster rate as compared to normal cells. With overcrowding of such cells, benign lump is formed, which is not harmful till the time cells don't invade into neighboring tissue. These cells are now termed as cancerous and lead to formation of tumor. Cancer cells are rebellious, unaffected by contact inhibition, multiply at a faster rate, show genetic abnormality, and above all consume major portion of cellular nutrients available. Metastasis is a process where cancer cells break off from the cancer site and are lodged into systemic circulation, followed by transit to different organs and adhere to them thus causing cancer at that site. With uncontrolled cell multiplication the quest for additional nutritional supply to the cancer cells is augmenting. Cancer cells suffice their metabolic needs via different pathways as compared to normal cells. The process of accumulating essential cellular components does not comply with normal cellular functioning as a result of different metabolic reprogramming [76-78].

FUTURE PERSPECTIVES

With the introduction of targeted drug therapy, a vast area for research was opened. Many researchers contributed in finding out various targets for drug delivery. The knowledge about the molecular structure of drugs, receptors, and different driver mutations have been the main pillars for developing a more advanced treatment regime. The development of newer drugs that are site specific have not only reduced the ill effects of chemotherapy, but also have provided the researchers with a platform to find out more targets and develop drugs accordingly. The early stages of lung cancer can be treated effectively as a result of this therapeutic progress. First line treatment modules for advanced neoplasm are proving to be effective with combination of drugs-based platinum and addition of drugs like bevacizumab leading the current treatment methods. Targeted therapies have so far been very useful for management of lung cancer. With the data obtained from various clinical trials and discovery of novel targets, the area for newer drug discovery and search for molecules that can effectively target driver mutations of all types, counter the processes that are important for cell proliferation and survival of cancer cell and also hinder the impact of immune checkpoints has certainly been on rise. Various clinical trials have helped in finding the best pick for targeting the driver mutations in lung cancer. Researchers are constantly working on predictive biomarkers and the possible mechanisms for acquired resistance for the targeted therapies. A lot of investigation has been made to date and researchers still find a wide scope for research in this area. The combination therapy is assumed to have a lot of potential to prove beneficial in coming years. By now it is anticipated that major of molecular targets have been recognized. The therapies which do not fit into the major tyrosine kinase receptor family will soon find its way into the market. These may be in the form of

combination therapies for driver mutations like BRAF and RET or HER2 mutations and many more.

One of the least explored mutation is KRAS, where so far, no suitable therapy has been accepted for treatment of patients, thus opening the way for researchers to explore this mutation at a deeper level. Various tumor suppressor genes also have not been explored extensively barring a few like TP-53 gene mutation. The quest for knowledge in this area will also be appreciable as there are no therapies that have proven effective for such suppressor gene mutations.

Immunotherapy is an emerging area in the treatment of lung cancer, offering wide scope for research as targets for immunotherapy have not been sufficiently tested. It can be anticipated that in future researchers may explore randomized trials as a major area for research. Trials like immunotherapy versus chemotherapy or combination of chemotherapy and antibodies for first line of treatment might prove to be the best way to determine the possible line of treatment for lung cancer. It can be foreseen that such trials will yield positive results and serve the purpose of combating lung cancer.

CONCLUSION

Despite advances in treatment for lung cancer with targeted therapy and immunotherapy being the torchbearers amongst treatment options and showing promising results, the wait for the best pick continues as many of the drugs either in targeted therapy or immunotherapy are in clinical trials and their effectiveness still needs to be validated. Moreover, secondary resistance has been a matter of concern for such therapies. Developing drugs, which can target multiple sites, and be effective against acquired resistance will surely be useful in reaching towards goal of treating lung cancer.

ACKNOWLEDGEMENT

Declared none.

CONFLICT OF INTEREST

The authors confirm no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not declared.

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

AUTHOR CONTRIBUTIONS

The entire study was conceptualized, designed and conducted the study with the help of other authors, wrote the first draft of the manuscript, and other authors contributed significantly to the revision of the manuscript. All Authors read and approved the final manuscript.

SOURCE OF FUNDING

Declared none.

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