Recent advancements in epidermal growth factor receptor (EGFR) inhibitors for the treatment of lung cancer

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Abstract:

Lung cancer is one of the top leading causes of deaths among people around the globe and tends to affect millions of individuals worldwide. People who smoke have the greatest risk of lung cancer, though lung cancer can also occur in people who have never smoked. The sundry treatment options available for the treatment of lung cancer includes following ways; Surgery, Chemotherapy, Targeted therapy, and Immunotherapy. Targeted therapy is a treatment that targets the cancer’s specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment blocks the growth and spread of cancer cells and limits damage to healthy cells. Targeted therapy for NSCLC includes; epidermal growth factor receptor (EGFR) inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, drugs targeting ROS1 genetic changes, drugs targeting NTRK fusion, drugs targeting BRAF V600E mutations, drugs targeting MET exon 14 skipping, drugs targeting RET fusion, and anti-angiogenesis therapy. Among these methods and targets, epidermal growth factor receptor (EGFR) inhibitors are considered to be most reliable and worthy targets for the treatment of lung cancer. The major classes of drugs under this includes: Osimertinib, Erlotinib, Afatinib, Dacomitinib, and Gefitinib.

Keywords: Cancer, lung cancer, targeted therapy, EGFR inhibitors.
INTRODUCTION

Cancer isn’t a single disease but is a huge family of diseases which can invade in any part of the body. It is usually characterised by abnormal and uncontrolled growth of cells, moreover sometimes tend to spread in other parts of the body as well, this process is known as metastasis and is the utmost reason for deaths of cancer’s patients making cancer as the 2nd most leading cause of mortality across the globe with approximately 10 million deaths in 2020. [1]

The most common types of cancers in males include colorectal, lung, liver, prostate, and stomach cancer. On the other hand, the most prevalent types of cancer in females comprise of breast, thyroid, cervical, lung, and colorectal cancer. [1]

![Fig. 1: The above pie chart represents the various types of cancers which were highly prevalent in the year 2020. Although above are the highly prevalent cancers, undeniably, the cancers causing highest number of deaths per year are camouflaged in these only. Where low and middle income countries comprises of an estimated 70% deaths of cancer’s patients. [1]](image-url)
Fig. 2: The above pie chart depicts the mortality data of cancer’s patients in the year 2020.

Transformation of normal healthy cells to tumour cells is multi-process succession of pre-cancerous lesion into malignant tumour gives rise to cancer. These alternations comes up as the output of patient’s genetic factors interconnection with either or more of the physical, chemical and biological carcinogens. [1]

<table>
<thead>
<tr>
<th>Physical carcinogens</th>
<th>Chemical carcinogens</th>
<th>Biological carcinogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultraviolet (UV) radiations</td>
<td>Arsenic</td>
<td>Oncogenic parasites:</td>
</tr>
<tr>
<td>Corpuscular radiations</td>
<td>Aflatoxin</td>
<td>Schistosoma Schistosoma</td>
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<tr>
<td>Electromagnetic radiations</td>
<td>Tobacco smoke</td>
<td>Hematobium</td>
</tr>
<tr>
<td>Low and high temperatures</td>
<td>Cadmium</td>
<td>Oncogenic bacteria:</td>
</tr>
<tr>
<td>Mechanical traumas</td>
<td>Trichloroethylene</td>
<td>Helicobacter pyroli bacilli</td>
</tr>
<tr>
<td>Solid and gel materials</td>
<td>N-methylcarbamate esters</td>
<td>Oncogenic fungi: Asperigillus falvus</td>
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<tr>
<td></td>
<td>N-Nitrosodimethylamine</td>
<td></td>
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<td></td>
<td>O-Aminoazotoluene</td>
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<tr>
<td></td>
<td>Polychlorinated biphenyls</td>
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<tr>
<td></td>
<td>2-Acetylaminofluorene</td>
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<tr>
<td></td>
<td>4-Aminobiphenyl</td>
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</tbody>
</table>

Cancers with highest number of mortality

- Lung Cancer - 1.80 million
- Colorectal Cancer - 0.935 million
- Liver Cancer - 0.830 million
- Stomach Cancer - 0.769
- Breast Cancer - 0.685 million

Lung Cancer - 1.80 million
Colorectal Cancer - 0.935 million
Liver Cancer - 0.830 million
Stomach Cancer - 0.769
Breast Cancer - 0.685 million
• 2-Napthylamine

Table 1: This table illustrates the various types of carcinogens. [1, 5]

The risks of cancer’s development in the body rises continuously with the increasing age. It is so because with age, the body’s overall system of repairing damaged cells decreases and thereby the system becomes weak. [1]

Lung Cancer

Being the 2nd most prevalent form of cancer, lung cancer reports millions of deaths every year in western and eastern countries globally [1, 6, 9]. It has been reported that people who fall in the age category of lesser than 40 years are less likely to develop lung cancer [10]. Smoking has always been pointed out as one of the substantial grounds for causing lung cancer in males and females of certain age groups [7, 13, 14].

There are basically two forms of lung cancer; Non-small cell lung cancer (NSCLC) and small cell lung cancers (SCLC) accounting for almost 85% and 15% of total lung cancer cases, correspondingly. These are the lung malignancies of non-smoking class which are usually categorised into squamous cell, large cell and adenocarcinoma [8, 11, 12, 13]. Among these, adenocarcinoma is most prevalent form of NSCLC and accounts for maximum number of patients i.e. 40% patients of lung cancer [12, 13].
Fig. 3: The above figure represents the lung cancer incidence rates in all ages of males and females, respectively [30].

**Diagnostic tests for Lung Cancer**

Almost all of the lung cancers are detected after they’ve started causing some sort of issues to the patient, rest of the cancers can be easily found with screening tests. Considering that the ultimate diagnosis of lung cancer is only done by testing and observing the sample of lung cells in laboratories. The diagnostic tests for lung cancer are basically divided into six different categories with further classifications. [2, 3]

<table>
<thead>
<tr>
<th>S.no.</th>
<th>Categories of tests</th>
<th>Various techniques for detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Imaging tests to look for lung cancer</td>
<td>Chest X-ray</td>
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<tr>
<td></td>
<td></td>
<td>Computed tomography (CT) scan</td>
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<td></td>
<td></td>
<td>Magnetic resonance imaging (MRI) scan</td>
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<tr>
<td></td>
<td></td>
<td>Positron emission tomography (PET) scan</td>
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<tr>
<td></td>
<td></td>
<td>Bone scan</td>
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<tr>
<td>2.</td>
<td>Tests to diagnose lung cancer</td>
<td>Sputum cytology</td>
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<tr>
<td></td>
<td></td>
<td>Thoracentesis</td>
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<tr>
<td></td>
<td></td>
<td>Needle biopsy</td>
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<td></td>
<td></td>
<td>Fine needle aspiration (FNA) biopsy</td>
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</tbody>
</table>
### Tests to find lung cancer spread in the chest

| Core biopsy | Transthoracic needle biopsy | Bronchoscopy | Endobronchial ultrasound | Endoscopic esophageal ultrasound | Mediastinoscopy and mediastinotomy | Thoracoscopy |

### Lung function tests (LFTs)

There are different types of LFTs, but they all comprise of making the patient breathe in and out through a tube that is connected to a machine that measures airflow.

### Lab tests of biopsy and other samples

| Molecular tests for gene changes | Tests for certain proteins on tumor cells |

### Blood tests

| Complete Blood Count (CBC) | Blood chemistry tests |

**Table 2:** The above table represents sundry techniques used for detection of lung cancers. [2,3]
## Treatment for NSC Lung Cancer

Sundry treatment options are available for NSCLC. The choice of treatment basically depends on the stage of NSCLC.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Surgery</td>
<td>Usually preferred for stage-I and II cancers when not contraindicated. Stages of cancer are indicated as per the severity and malignancy of the cancer.</td>
</tr>
<tr>
<td>2.</td>
<td>Neoadjuvant Chemotherapy</td>
<td>Beneficial for early treatment of micrometastases, and down staging of tumour.</td>
</tr>
<tr>
<td>3.</td>
<td>Adjuvant Chemotherapy</td>
<td>It is indicated in patients with stage-II and III-A disease after surgical resection has been done.</td>
</tr>
<tr>
<td>4.</td>
<td>Immunotherapy</td>
<td>Used for the management of Stage-III NSCLC where surgical resection can’t be performed.</td>
</tr>
<tr>
<td>5.</td>
<td>Chemotherapy for advanced stages of cancer</td>
<td>It is generally preferred for patients who possess metastatic cancer which requires systemic treatment.</td>
</tr>
<tr>
<td>6.</td>
<td>Targeted therapy</td>
<td>It targets the cancer’s specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This blocks the growth and spread of cancer cells and limits damage to healthy cells. Targeted therapy for NSCLC includes;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Epidermal growth factor receptor (EGFR) inhibitors,</td>
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<td></td>
<td></td>
<td>- Anaplastic lymphoma kinase (ALK) inhibitors,</td>
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<tr>
<td></td>
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<td>- Drugs targeting ROS1 genetic changes,</td>
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<td></td>
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<td>- Drugs targeting NTRK fusion,</td>
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<td></td>
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<td>- Drugs targeting BRAF V600E</td>
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</tbody>
</table>
mutations,
- Drugs targeting MET exon 14 skipping,
- Drugs targeting RET fusion, and anti-angiogenesis therapy.

Table 3: The above table illustrates the various types of treatment options available for treatment of NSCLC. [13, 15, 26, 27, 28, 29]

The Epidermal Growth Factor Receptor (EGFR) Pathway in Non-Small Cell Lung Cancer (NSCLC)

The Epidermal Growth Factor Receptor (EGFR) - ErbB1 is a trans- membrane tyrosine kinase receptor is one of the family members of ErbB receptors, where other members comprises of; ERBB2 (HER2/neu), ERBB3 (HER3), and ERBB4 (HER4). [4, 16, 17]

An extracellular ligand-binding domain, a trans-membrane domain, and a cytoplasmic domain carrying tyrosine auto-phosphorylation sites in the tyrosine kinase zone, are the three main characteristic features of EGFR’s structure [18, 19]. EGFR goes through auto-dimerization and dimerization with other members of ErbB receptors family following after the ligand binding. [14, 31]

18-24 exons are clustered around the ATP-binding pocket of the enzyme and encode the EGFR kinase domain. Among these, 18-21 are the exons where most of the mutations take place. Dimerization and ligand binding are important pre-requisites which help in triggering the EGFR signalling with targeted functions [14, 32, 33]. Therefore, these results in EGFR’s increased kinase activity, directing the increased potential activation of downstream pro-survival signal pathways that enhances the NSCLC cells’ tumour-genesis [20].

Interleukin 6(IL-6)/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK), and phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR are the three major downstream signalling pathways that are activated by EGFR [16, 17, 20].

Almost 90% of the total EGFR mutations are accounted by two types of mutations i.e. L858R and exon-19 deletion. In addition, T790 mutation is also seen in few of the cases. L858R are point mutations in exon-21 resulting in substitution of arginine in place of leucine at codon- 858. Furthermore, exon-19 deletion is simply the in- frame deletions in exon 19 [21-24].
EGFR-tyrosine kinase inhibitors (TKIs) comprising of gefitinib, erlotinib (1st generation EGFR-TKI), afatinib, dacomitinib (2nd generation EGFR-TKI), and osimertinib (3rd generation EGFR-TKI) have shown potential activity in preventing the EGFR L858R or exon 19 deletion mutations.\[4, 21, 22, 23, 24, 25\]

Fig. 4: The above figure represents the Epidermal Growth factor receptor (EGFR) pathway in non-small cell lung cancer. [4]
Targeting EGFR in Lung Cancer

It has been found through several systemic researches that EGFR can be considered as a novel target for the treatment of lung cancer [34]. The considerable approaches used for inhibition of EGFR are: a) Inactivation of intracellular TK signalling, and b) Neutralizing antibodies used against EGFR and its ligands.

![Diagram showing EGFR pathway inhibition](image)

Fig. 5: EGFR-TK-inhibitors inhibiting the EGFR pathway ultimately blocking the lung cancer cells’ proliferation [35, 36].

Erlotinib and Gefitinib are the most thoroughly considered EGFR-TK inactivators for Lung Cancer [37, 38]. Whereas, EGFR functioning is blocked by using monoclonal antibodies such as Cetuximab and Bevacizumab [39, 40]. Above are the types of effective EGFR
inhibitors for hindering proliferation of malignant cells of lung cancer, increasing apoptosis, and decreasing the metastasis of lung cancer [39, 41].

### EGFR Inhibitors

<table>
<thead>
<tr>
<th>S.no.</th>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Erlotinib</td>
<td><img src="image" alt="Erlotinib Structure" /></td>
</tr>
<tr>
<td>2.</td>
<td>Gefitinib</td>
<td><img src="image" alt="Gefitinib Structure" /></td>
</tr>
</tbody>
</table>
3. Afatinib

![Afatinib structure]

4. Icotinib

![Icotinib structure]

Table 4: The above table shows the various EGFR inhibiting drugs available for the treatment of lung cancer. [42, 43, 44, 45]

- **Erlotinib**

Erlotinib principally works through inhibiting the tyrosine phosphorylation by stopping up the intracellular ATP binding site of EGFR [46, 47]. The various extensive adverse side effects related to Erlotinib are, particularly on skin, intestine and eyes. Therefore, over a period of time it’s been suggested to go for reduced doses and treatments with fixed time intervals to avoid and manage toxic effects of Erlotinib [48]. The specific roles of erlotinib in treating NSCLC and SCLC in patients were proven by clinical trials. [46] Survival rates of NSCLC patients were improved using Erlotinib when compared to the single-line chemotherapy [49]. On the other hand, Erlotinib was found to be much effective when used in the second line treatment of old aged NSCLC patients [50, 51]. The two line treatment undoubtedly improved the patients’ health by relieving the
symptoms of respiratory uneasiness, cough, chest pain and sundry discomforts [52]. A potential effectiveness in the treatment was shown by Erlotinib when used in combination with permetrexed and docetaxel chemotherapeutics [14, 53]. Nonetheless, Erlotinib was found to be the most effective third line treatment for the patients with declined performance in health improvement [53]. Erlotinib didn’t only ameliorate patients’ life but also improved lung cancer’s palliative symptoms with adequate drug toleration as a third line treatment [54, 55, 56].

• Gefitinib

On the basis of the data obtained from the clinical trials, Food and Drug Administration (FDA) countersigned Gefitinib in 2003 as a 3rd line treatment [38]. It was reported that in phase II, as well as in phase III, the drug was effectively able to prevent metastasis, where many different chemotherapies had failed [57]. Surprisingly, in phase III trial, 250 mg/Kg Gefitinib was failed when discussed about the overall survival of 1,700 patients [58]. These reports ultimately made FDA to think over the mandatory use of Gefitinib for the pre-treated patients of cancer [14, 46, 58]. Remarkably, it was found that Gefitinib had very less number of side effects and was adequately tolerated when compared to other drugs of chemotherapies [59]. Certain disadvantages were also seen with the continued use of first line EGFR-TK inhibitors, though Erlotinib and Gefitinib were perfect to be used as second and third line drugs for treatment of Lung cancer [60]. Significant resistance was seen with the use of Erlotinib and Gefitinib [61-63]. Therefore, to avoid such cons, second line drugs (Afatinib) were proposed for better treatment of Lung cancer [60].

• Afatinib

Afatinib principally works by binding to 773, 803, and 805 cystine residues of EGFR-TK [64, 65]. It was basically found effective against resistances which were shown in case of Erlotinib and Gefitinib, and in cells with T790M and HER2 mutations within EGFR’s gene [64, 66]. Certain side effects such as severe diarrhoea, mouth ulcers, skin rashes, upset stomachs, etc. were reported during the studies of Afatinib [60, 67, 68]. Afatinib, when used in combination with other drugs showed remarkably enhanced progressive survival result, as compared to single drug therapy [67]. Afatinib and cetuximab combination was found to be much effective in place where a co-treatment of Erlotinib or Gefitinib failed when used with tyrosine kinase (TK) monoclonal antibody (Cetuximab) [64]. The reason in the failure of Erlotinib or Gefitinib with Cetuximab lies in the development of T790M mutation in EGFR’s genes which can be easily treated using combination of Afatinib and Cetuximab [69]. Nevertheless, Afatinib too possesses the risk to develop resistance in patients with lung cancer [60, 64, 70].

• Icotinib

Icotinib has found its use in the treatment of patients who suffered from NSCLC with brain metastasis during the diagnosis and treatment [71]. Other drugs used in Chemotherapies crashed to cross the BBB (Blood Brain Barrier). Moreover, Erlotinib, Gefitinib and Afatinib were only able to reach by the outer cranial lesions [72]. In
addition, it has been reported that Icotinib not only effective for brain metastasis, but also for the sundry EGFR mutations seen in patients [14, 73, 74, 75]. The various side effects seen in patients includes acne, lesions, and diarrhea, however, all side effects were non-severe and didn’t cause any sort of liver damage. Overall, it can be easily stated that Icotinib isn’t only potent, but also safer for advanced NSCLC with brain metastasis [76]. There are others drugs too going in different phases of the clinical trial which could be used for the treatment of lung cancer in future if found to be safe and effective.

Conclusion:

With the advancement of time, Cancer has taken up more disastrous and deadly forms. The limited options available for the treatment or cure, has always stood as a thrilling challenge for the physicians as well as for the patients. Despite the growing challenges, Science too has evolved into a lot more and has been able to give potential drug candidates for the treatment of lung cancer. Looking on the potency, efficacy and less number of side effects of the EGFR inhibitors, these drugs have come up forward for the effective treatment of Lung Cancer. Though, owing to the limited options in this category, still many researches and studies need to be carried out in order to achieve the desired level of treatment in patients and hopefully, all the challenges would soon be come across.

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