Role of EGFR Inhibitors in Lung Cancer

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Abstract
Lung cancer, also known as lung carcinoma (since about 98–99% of all lung cancers are carcinomas), is a malignant lung tumor characterized by uncontrolled cell growth in tissues of the lung. Lymphomas and melanomas (from lymphoid and melanocyte cell lineages) can also rarely result in lung cancer. In 2005, the total number of new lung cancer cases in China was over 500,000. According to GLOBOCAN 2012, lung cancer is the most common malignancy and cause of cancer mortality in China, representing 21% of all cancers and 27% of all cancer-related deaths. Lung cancer incidence and mortality is higher in eastern China and in urban areas, which has been attributed to westernization of lifestyle. EGFR is a transmembrane tyrosine kinase receptor, which is one of the ErbB family of receptors. The ErbB family includes EGFR (ErbB1), ERBB2 (HER2/neu), ERBB3 (HER3), and ERBB4 (HER4). Also known EGFR tyrosine kinase inhibitor, epidermal growth factor receptor inhibitor. EGFR kinase domain mutations including exon 19 deletion, L858R and T790M increase kinase activity of EGFR, leading to the hyperactivation of downstream signaling pathways including MAPK, PI3K/Akt/mTOR, and IL-6/JAK/STAT3 which promote tumorigenesis of NSCLC cells.

Keywords - Lung cancer, EGFR, EGFR inhibitor, EGFR – TKIs

1. Introduction
Lung cancer, also referred to as lung carcinoma (because 98–99% of all lung cancers are carcinomas), is a malignant lung tumour characterised by unchecked cell proliferation in lung tissues. Cancerous epithelial cells that have undergone transformation or tissues made up of epithelial cells are where lung carcinogenesis occurs. Other types of lung cancer, including the rare sarcomas of the lung, are caused by mesenchymal cells’ malignant alteration of connective tissues (such as nerve, fat, muscle, and bone). Rarely, lung cancer can also originate from melanomas, lymphomas (originating from lymphoid and melanocyte cell lineages, respectively [1].

1.1 Signs and Symptoms of lung cancer[51]
- Cough
- Shortness of breath (dyspnea)
- Chest pain
- Wheezing
- Coughing up blood (hemoptysis)
- Hoarseness
- Loss of appetite
- Weight loss
- Swelling in the face, neck arm

Figure 1: Lung Cancer

1.2 Risk factors of lung cancer
- Smoking
1.3 Types of lung cancer
There are mainly two types
1. Small cell lung cancer (SCLC)
2. Non-small cell lung cancer (NSCLC)

1. Small cell lung cancer
Compared to NSCLC, small cell lung cancer (SCLC) grows more rapidly and is more difficult to cure. It is frequently identified as a very tiny lung tumour that has migrated to other areas of your body. Small cell carcinoma (also known as oat cell carcinoma) and mixed small cell carcinoma are two particular kinds of SCLC[2].

2. Non-small cell lung cancer
Lung cancer is most frequently diagnosed as non-small cell lung cancer (NSCLC). More than 80% of lung cancer cases can be attributed to it. Squamous cell carcinoma and adenocarcinoma are frequent forms. The less frequent NSCLC subtypes are adenosquamous and sarcomatoid carcinoma[3].

1.4 Active cases of lung cancer in the world
Brazil, Russia, India, China, and South Africa are recognized for their large and fast-growing economic[3], Brazil where lung cancer mortality among men peaked in 1993 and tobacco use peaked in the 1970s, is one of the few South American nations with a cancer registry and continues to rise among women[4,5]. Similar to the United States, the Russian Federation has very high rates (60%) of both smoking and alcohol usage, compared to substantially lower levels for women[6]. As a result, Russia has one of the lowest rates of lung cancer mortality for women among all European nations, but the highest rate for males. After reaching an all-time high in the early 1990s, mortality is currently dropping, but tobacco use continues to be a significant obstacle to effective cancer control[7]. Environmental pollution, occupational exposure to nuclear reactors, and asbestos mine exposure are additional risk factors in Russia[6]. Comparatively, lung cancer incidence and mortality rates in India are among the lowest in the world[8]. The most common cancers in men are head and neck, gastric, and esophageal cancers, linked to heavy smokeless tobacco use, breast and cervical cancer in women are the most prevalent types. Squamous cell lung cancer was found to be the most prevalent histology overall and among smokers, according to one study from northern India[9]. While cigarette smoking (hand-rolled tobacco) is the most widely used tobacco product (92%), whereas cigarette smoking has a reported prevalence range of 28 to 57% among men[10]. Over 500,000 new lung cancer cases were reported in China in 2005. According to GLOBOCAN 2012, lung cancer accounts for 21% of all cancer deaths in China, making it the most prevalent cancer and the main cause of cancer mortality[6]. Eastern China and urban areas have higher rates of lung cancer incidence and mortality, which has been linked to the westernisation of lifestyle[11]. However, mortality rates are rising more quickly in rural regions because of the lack of access to healthcare[6]. In addition, lung cancer incidence rates are rising more quickly among women than among Chinese males, who smoke 68% of the time and have higher age-adjusted mortality rates[12]. Secondhand smoking, air pollution, and domestic use of biomass fuels are risk factors for Chinese women[13].

1.5 Classification of Anti Lungs Cancer Drug [14]:
1. Drugs Used in the treatment of small cell lung cancer
   E.g
   • Atezolizumab
   • Doxorubicin hydrochloride
   • Lubrinitedcin
   • Methotrexate sodium
   • Trexall
   • Nivolumab

2. Drugs Used in the treatment of non-small cell lung cancer
   E.g
   • Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation)
   • Afinitor (Everolimus)
   • Atezolizumab
   • Bevacizumab
   • Docetaxel
   • Gefinitib
1.6 EGFR (Epidermal growth factor receptor): -

A member of the ErbB family of receptors, EGFR is a transmembrane tyrosine kinase receptor. EGFR (ErbB1), ERBB2 (HER2/neu), ERBB3 (HER3), and ERBB4 (HER4) are all members of the ErbB family. EGFR is a trans-membrane glycoprotein that controls signalling pathways to restrain cellular proliferation. It has an intracellular tyrosine kinase domain and an extracellular epidermal growth factor binding domain. Some lung malignancies have been linked to mutations in epidermal growth factor receptors.

The epidermal growth factor receptor (EGFR) regulates the development and homeostasis of epithelial tissues. Breast, lung, esophageal, head and neck, and other cancers express the broad family of receptor tyrosine kinases (TK) known as epidermal growth factor receptors (EGFRs). The main players in a complex signalling cascade that controls the proliferation, signalling, differentiation, adhesion, migration, and survival of cancer cells are EGFR and members of its family. EGFR and its family members have become desirable candidates for anti-cancer therapy due to their multifaceted roles in the development of cancer.

1.7 EGFR inhibitor:-

An epidermal growth factor receptor is a compound that prevents a protein from acting (EGFR). Some normal cells have EGFR on their surface, and this protein is crucial in cell proliferation. It may also be present in some types of cancer cells at high concentrations, which stimulates the growth and division of these cells. The growth of cancer cells may be stopped by blocking EGFR. To treat cancer, some EGFR inhibitors are employed. These include erlotinib, gefitinib, cetuximab, and necitumumab.

Overexpression of EGFR encourages gene amplification and mutation, which have an impact on tumor-induced neoangiogenesis, invasion, and metastasis as well as cell proliferation and survival.

1.8 Classification of EGFR inhibitor:-

EGFR inhibitors can be classified into two types:

1. Tyrosine kinase inhibitors (TKI): these bind to the tyrosine kinase domain in the epidermal growth factor receptor and stop the activity of the EGFR.
   - eg, erlotinib, gefitinib
2. Monoclonal antibodies: these bind to the extracellular component of the EGFR and prevent epidermal growth factor from binding to its receptor, therefore preventing cell division.
   - eg, cetuximab, necitumumab

Classification of Approved EGFR-TKIs
Classifications of the EGFR-TKIs, which received global approval for clinical use. In the following, the EGFR-targeting drugs are classified based on their chemistry, clinical use, target kinases, and the type of inhibition/interaction with EGFR.

A. Chemical classification

B. Classification based on the type of interaction with EGFR

C. Classification based on clinical use

D. Classification based on target kinase

E. Classification based on generation

A. Chemical classification

The three subclasses of approved EGFR-TKIs can be categorised based on their chemical structures. The aminopyrimidine derivatives, which comprise the drugs almonertinib, brigatinib, and osimertinib, make up the first subclass. Ibrutinib is regarded as a fused aminopyrimidine derivative in this study. The second category consists of two derivatives, neratinib and pyrotinib, both of which have a quinoline-4,6-diamine nucleus. The third group is the quinazoline-4,6-diamine-based derivatives which include afatinib, dacomitinib, erlotinib, nicotinic, lapatinib, imatinib, and vandetanib, shown in Figure 3.\(^{[22]}\)

![Chemical classification of EGFR-TKIs](image)

**Figure 3:** Chemical classification of EGFR-TKIs

B. Classification based on the type of interaction with EGFR inhibitor

The approved EGFR-TKIs can also be divided into reversible and irreversible inhibitors according on how the activity shown the first kind, noncovalent interactions involving electrostatic, hydrogen-bonding, and hydrophobic contacts allow the inhibitors to competitively bind to the EGFR's ATP binding site.\(^{[23]}\)
In the second type, the cysteine residue in the EGFR forms a covalent bond with the EGFR inhibitors. The presence of an electrophilic side chain that functions as a Michael acceptor and chemically combines with the cysteine thiol group to generate a covalent adduct characterises the structure of these inhibitors.\(^24\).

**C. Classification based on clinical use**

Based on the kinds of malignancies for which they have been given approval, the EGFR inhibitors can also be divided into three groups.\(^25\) Afatinib, almonertinib, brigatinib, dacomitinib, erlotinib, gefitinib, icotinib olmutinib, and osimertinib are some of the medications that have been approved for the treatment of NSCLC. The second category consists of breast cancer medications including lapatinib, neratinib, and pyrotinib. The third category, however, consists of medications licenced for treating various malignancies, including solid tumours, pancreatic cancer, and thyroid cancer (erlotinib), pancreatic cancer, and thyroid cancer (vandetanib) (simotinib).

**D. Classification according to target kinase**

The authorised EGFR-TKIs can also be divided into the following categories:

1. Selective EGFR inhibitors, which have a high degree of selectivity for the EGFR target and include gefitinib
2. Lapatinib, which inhibits both EGFR and ErbB-2, is a dual EGFR inhibitor.
3. Brigatinib, Pyrotinib, and Vandetanib are multi-kinase inhibitors.

In addition to the EGFR, these medicines exhibit broad-spectrum activity against a number of additional kinases.\(^26\)

**E. Classification based on generation**

Among the approved EGFR-TKIs, are classified according to generation EGFR inhibitors, as shown in Figure 5.
1) **First generation:** The drug in this class bind reversibly to the PTK domain of the EGFR, which prevents ATP from binding to the EGFR and, as a result, prevents EGFR activation and cell growth[27].
   E.g. Gefitinib, erlotinib, lapatinib, and icotinib
2) **Second generation:** The drugs contain a Michael acceptor site which allows them to bind covalently to the EGFR, leading to the irreversible inhibition of the kinase activity, which provides an advantage over first-generation EGFR-TKIs[28].
   E.g. afatinib, neratinib, and docamitinib
3) **The third generation:** The chemical structures of these drugs include a pyrimidine nucleus attached to a substituted aniline or phenoxy moiety. These moieties bear an acrylamide group that, as noted above, can form a covalent bond with the cysteine residue in the EGFR[29].
   E.g. almonertinib, olmutinib, and osimertinib
4) **Multi-kinase inhibitor:** Due to their inhibitory activities against kinases other than the EGFR[30].
   E.g. Brigatinib, vandetanib, and pyrotinib

### 1.9 Mechanism of EGFR inhibitor:

The EGFR mutation is well established as the primary oncogenic-driven mutation in some NSCLCs, and the activating mutation in the EGFR kinase domain has received much research[31]. The primary three downstream signalling pathways that EGFR activates are interleukin 6 (IL-6)/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signalling pathways, phosphatidylinositol 3-kinase 3-kinase (PI3K)/Akt/mTOR, and mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK)[ Exon 19 deletion and L858R (point mutations in exon 21 that result in a leucine to arginine substitution at codon 858) are two different forms of EGFR mutations[34,35].

**First-generation EGFR TKIs**
The first-generation EGFR-TKIs gefitinib and erlotinib are inert against acquired T790M mutation but have reversible binding to mutant EGFR[36,37]. For patients with sensitive EGFR mutations who have advanced NSCLC, EGFR-TKIs have been routinely used as the first-line standard treatment (L858R or exon 19 deletions). The T790M mutation is a point mutation in exon 20 that changes the amino acid at position 790 from methionine to threonine.

**Second-generation EGFR TKIs**
The second-generation EGFR-TKIs afatinib and dacamitinib have irreversible covalent binding to all ErbB receptors (EGFR, ErbB2, ErbB4, and ErbB heterodimers), and they are inactive to the T790M mutation[38,39]. The T790M mutation is referred to as a "gate keeper" mutation in the kinase domain of EGFR, and it affects the Among NSCLC patients who acquired resistance to the first and second generation of EGFR-TKIs, 30–60% of secondary EGFR point mutations include T790M mutations[40,41].

**Third-generation EGFR TKIs**
As a third-generation EGFR-TKI, osimertinib is activated by the T790M mutation and is distinguished by its irreversible covalent binding to mutant EGFR[40,41]. In order to focus on the T790M mutation, numerous third-generation EGFR inhibitors are presently being developed. These medications, unlike second-generation TKIs, are well tolerated and have few adverse effects on wild-type EGFR because they are more selective for T790M and mutant EGFR than wild-type EGFR. Osimertinib (AZD9291), among them, was the first to be approved by the FDA and EMA in November 2015 and February 2016, respectively, for metastatic EGFR T790M+ NSCLC that had advanced during or following EGFR TKI therapy.

In addition, the role of therapies such as immune checkpoint inhibitors (ICIs) in combination with or sequentially following EGR-TKIs, remains to be explored. The oncogenic pathway of EGFR and the targeting EGFR mutations of EGFR-TKIs are summarized in figure 6.
Figure 6: The Epidermal growth factor receptor (EGFR) pathway in non-small cell lung cancer (NSCLC). EGFR kinase domain mutations including exon 19 deletion, L858R, and T790M increase the kinase activity of EGFR, leading to the hyperactivation of downstream signaling pathways including MAPK, PI3K/Akt/mTOR, and IL-6/JAK/STAT3 which promote tumorigenesis of NSCLC cells. The three generations of EGFR-TKIs differ with respect to how they bind to different EGFR mutations and which EGFR mutations are active or inactive.

1.10 Lung cancer therapy:
Lung cancer therapy included:
1. Surgery
2. Radiation therapy
3. Chemotherapy
4. Targeted drug therapy
5. Immunotherapy

1. Surgery:
Your surgeon performs surgery to remove the lung cancer along with a margin of healthy tissue. Procedures to remove lung cancer include:
- **Wedge resection**, which involves removing a tiny portion of the lung that includes the tumor together with a margin of healthy tissue.
- **Segmental resection** which involves removing a greater segment of the lung rather than an entire lobe.
- **Lobectomy** which involves removing one lung's whole lobe.
- **Pneumonectomy** to remove an entire lung.

Your thoracic lymph nodes may be removed during surgery so that your surgeon can examine them for cancerous growths. If your cancer has spread outside of your lungs, surgery can be a possibility. In order to decrease a larger lung cancer before surgery, your doctor may advise chemotherapy or radiation treatment. After surgery, your doctor might advise chemotherapy or radiation therapy if there's a chance that cancer cells were left behind or if your cancer might return[42].
2. **Radiation therapy**:–

To kill cancer cells, radiation therapy uses extremely powerful energy beams from sources like X-rays and protons. You lie on a table while receiving radiation therapy, with a machine moving around you to target certain areas of your body. Radiation therapy may be able to ease symptoms like pain for advanced lung tumours and those that have spread to other parts of the body[42]. Different radiotherapy (RT) techniques, such as stereotactic body radiotherapy (SBRT), intensity-modulated radiotherapy (IMRT), and three-dimensional (3D) conformal radiotherapy (CRT), have been used to plan and administer radiation to the tumour (SBRT).

Directing the radiation dose to the target due to tumour motility and anatomical change during treatment is one of the many difficulties with RT in thoracic neoplasms. Four-dimensional (4D) imaging, one of the more advanced RT technologies, enables the formulation of a tailored treatment plan that delivers enough doses directed at the target while preserving the nearby vital normal tissues[43]. Ionizing radiation, which is employed in RT, can be produced by electromagnetic radiation, photon radiation (such as x-ray and gamma radiation), as well as particle radiation (alpha, neutron, proton, and electron). Ionizing radiation produces electrons. In its target, ionising radiation induces electron ejection, which results in energy loss to the medium on a magnitude comparable to LET (linear energy transfer). With many charges, a low-speed particle has a high LET[44].
3. **Chemotherapy:**
   Drugs are used in chemotherapy to kill cancer cells. It is possible to get one or more chemotherapy medications intravenously or orally. A mixture of medications is typically administered in a series of treatments spread out over weeks or months, with intervals in between to allow for recovery\[^{42}\]. These include altered cellular targets for chemotherapy, lower drug concentrations inside cells, blocking chemotherapy-induced cell cycle arrest and apoptosis, developing phenotypes resembling cancer stem cells and the epithelial-mesenchymal transition, dysregulated microRNA expression, epigenetic manipulation, and interactions with tumour microenvironments\[^{43}\].

4. **Targeted drug therapy:**
   Targeted medication therapies concentrate on particular defects found in cancer cells. Targeted medication therapies can kill cancer cells by obstructing these aberrations. Some targeted medicines are only effective in patients whose cancer cells contain specific genetic abnormalities\[^{42}\].
   
   EGFR inhibitors used in NSCLC with EGFR gene mutations
   - Erlotinib (Tarceva)
   - Afatinib (Gilotrif)
   - Gefitinib (Iressa)
   - Osimertinib (Tagrisso)
   - Dacomitinib (Vizimpro)\[^{46}\].

5. **Immunotherapy:**
   Immunotherapy fights cancer by activating your immune system. Because cancer cells create proteins that assist them conceal themselves from immune system cells, your body's immune system, which fights disease, may not attack your cancer. Immunotherapy works by obstructing that procedure. Treatments using immunotherapy are typically only prescribed to patients with locally advanced lung cancer and cancer that has progressed to other body parts\[^{42}\]. When combined with other immunotherapies such immune checkpoint inhibition, the identification of the best potential neoantigens may enhance the effectiveness of cancer vaccines and open the door to customised immunotherapy\[^{47}\].

1.11 Novel drug approved by FDA 2021-22:
- **Drug approved in 2021**\[^{48}\]
  1. Mobocertinib (Exkivity®) – September 2021
  2. Sotorasib (Lumakras™) - June 2021
  3. Amivantamab-vmjw (Rybrevant™) - May 2021
  4. Lorlatinib (Lorbrena®) - March 2021
  5. Cmiplimab-rwlc (Libitayo®) - Feb 2021
  6. Trilaciclib (cosela™) - Feb 2021
  7. Tepotinib (Tepmetko®) - Feb 2021

- **Drug approved in 2022**\[^{49}\]
Drugs of this type include those that target the epidermal growth factor receptors of epidermal cells (EGFR inhibitors).

II. Conclusion :-

Accumulating evidence suggests that exon 19 deletions and L8585R are two different disease entities. Therapeutic strategies should differ when treating lung adenocarcinoma harboring exon 19 deletions or L858R mutations. This study reveals that in patients with advanced NSCLC harboring exon 19 deletions, both reversible and irreversible TKIs are associated with better OS compared with conventional chemotherapy.

III. Reference :-

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