Indian J. Pharm. Biol. Res. 2015; 3(2):81-87

CODEN (USA): IJPB07 ISSN: 2320-9267

Indian Journal of Pharmaceutical and Biological Research (IJPBR)

Journal homepage: www.ijpbr.in

Review Article

Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-small cell lung cancer

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ARTICLE INFO:

Article history:

Received: 6 April 2015
Received in revised form:
10 May 2015
Accepted: 5 June 2015
Available online: 30 June 2015

Keywords:

NSCLC **(**Non-small cell lung cancer); tyrosine kinase inhibitor; EGFR (endothelial growth factor receptor); VEGFR (vascular endothelial growth factor receptor)

ABSTRACT

Aberrant increased expression and activation of receptor tyrosine kinases occur frequently in human carcinomas. Several small molecules targeting receptor tyrosine kinases, which have crucial roles in the growth factor signaling that promote tumor progression in various malignancies, including non-small cell lung cancer (NSCLC), are currently in clinical development. Therapeutic strategies include inhibition of growth factor tyrosine kinase function. Drugs of this type include those that target the epidermal growth factor receptor tyrosine kinase, those that target vascular endothelial growth factor receptors tyrosine kinase and those that target anaplastic lymphoma receptor tyrosine kinase. In this review we first discuss the role of receptor tyrosine kinases in human malignancies, and focus on discussing the potential use of epidermal growth factor receptor tyrosine kinase inhibitors and the vascular endothelial growth factor receptors tyrosine kinase inhibitors in NSCLC. In addition, we discuss the contribution of growth factor receptor tyrosine kinase inhibitors to the clinically observed resistance, and toxicity.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide and constitutes approximately 85% of all lung cancers [1, 2]. The vast majority of patients with advanced NSCLC are not curable and overall five year survival is 14% (Stage IIIA), 5% (Stage IIIB), and 1% (Stage IV) [3]. Chemotherapy, a category of cancer treatment that uses chemical substances, especially one or more anti-cancer drugs is beneficial for patients with locally advanced and metastatic disease. Numerous phase III studies have determined the superiority of systemic chemotherapy over best supportive care. Platinum based chemotherapy has been widely accepted as the standard of care for the initial treatment of advanced NSCLC [4]. However first line chemotherapy is modest at best and with substantial toxicity. Clearly a different approach is needed for the treatment of NSCLC.

Protein kinases are key regulators of cell function that contribute one of the largest and most functionally diverse genes families. By adding phosphate groups to substrate proteins, they direct the activity, localization and overall function of many proteins, and serve to orchestrate the activity of almost all cellular processes. Kinases are particularly prominent in signal transduction and co-ordination of complex functions such as the cell cycle. Tyrosine kinase forms a significant share of all oncoproteins thus they take centre stage as possible targets for cancer therapy. The recent discovery of tyrosine kinase driver mutations as a therapeutic target for cancer and ATP-binding domain of tyrosine kinases have led to clinical development of many tyrosine kinase inhibitors in various malignancies, including lung cancer [5-7].

In recent years, knowledge about the roles of protein tyrosine kinases in progression, metastasis, and growth at the metastatic site in NSCLC and the understanding of NSCLC as a heterogeneous disease with several genetic subsets have also received considerable attention, and have led to an improvement of patients treatment outcome. In the following we will discuss tyrosine kinase, epidermal growth factor receptor tyrosine kinase inhibitors and vascular endothelial growth factor receptor inhibitors in NSCLC.

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Tyrosine Kinase

A tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to a protein in a cell. It functions as an "on" or "off" switch in many cellular functions. Tyrosine kinases are a subclass of protein kinase. Tyrosine kinases are a subgroup of the larger class of protein kinases that attach phosphate groups to other amino acids (serine and threonine) [8, 9]. Phosphorylation of proteins by kinases is an important mechanism in communicating signals within a cell (signal transduction) and regulating cellular activity, such as cell division. Protein kinases can become mutated, stuck in the "on" position, and cause unregulated growth of the cell, which is a necessary step for the development of cancer. Therefore, kinase inhibitors, such as imatinib, are often effective cancer treatments. Most tyrosine kinases have an associated protein tyrosine phosphatase, which removes the phosphate group. Tyrosine kinases function in a variety of processes, pathways, and actions, and are responsible for key events in the body. The receptor tyrosine kinases function in transmembrane signaling, whereas tyrosine kinases within the cell function in signal transduction to the nucleus. Ligand binding to the extracellular domain of the receptor promotes receptor dimerization, resulting in autophosphorylation of specific tyrosine residues of the cytoplasmic kinase domain. Besides these phosphorylation sites for regulation of their own kinase activity, other phosphorylation sites of kinases are being used to control protein interactions. The activated receptor recruits interacting proteins that bind to certain phosphorylation sites. Recruited and phosphorylated signaling proteins are subsequently able to phosphorylate other proteins [10, 11]. Activation of (multiple) signaling pathways eventually leads to biological responses such as cell activation, proliferation, differentiation, migration, survival, and vascular permeability (**Figure 1**).

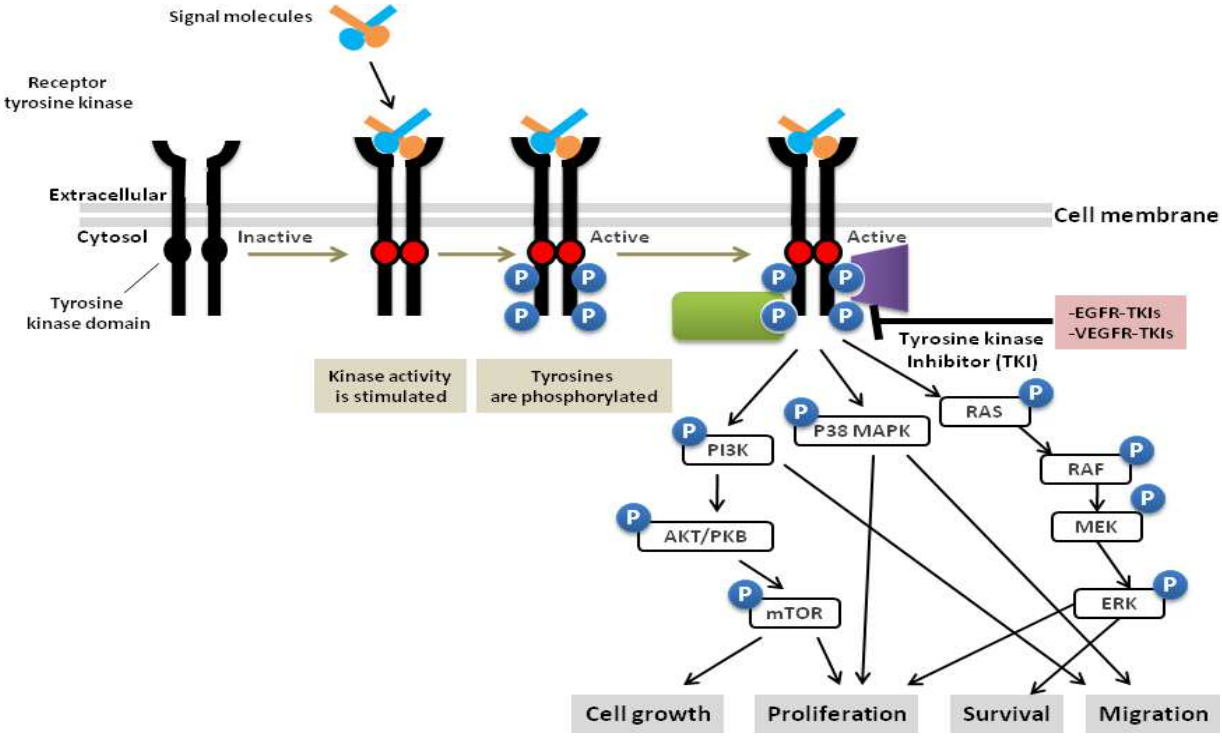

Figure 1: Tyrosine kinase signaling and associated growth factor receptors. On activation (by growth factor binding), the growth factor receptor such as EGFR and VEGFR authophosphorylates tyrosine residues in its cytoplasmic domain, which serve as a docking sites for the assembly of protein complexes that transduce EGF or VEGF signals to generate specific biological responses.

EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS

Epidermal growth factor receptor (EGFR) belongs to a family of receptor tyrosine kinases (RTKs) that include EGFR/ERBB1, HER2/ERBB2/NEU, HER3/ERBB3, and HER4/ERBB4. In normal cells, the binding of ligands, such as epidermal growth factor (EGF), induces a conformational change that facilitates receptor homo- or heterodimer formation, thereby resulting in activation of EGFR tyrosine kinase activity [12]. Activated EGFR then phosphorylates its substrates, resulting in activation of multiple downstream pathways within the cell, including the PI3K-AKT-mTOR pathway, which is involved in cell survival, and the RAS-RAF-MEK-ERK pathway, which is involved in cell proliferation (Figure 1) [13-15]. EGFR is overexpressed in the majority of NSCLC and it is an important target in the treatment of NSCLC and EGFR associated signaling pathways

are frequently dysregulated. EGFR is involved in regulation of numerous oncogenic functions such as cell proliferation, survival, differentiation, neovascularisation, invasion and metastasis. Activating mutations in *EGFR* lead to constitutive tyrosine kinase activation and oncogenic transformation of lung epithelial cells *in vitro* [16, 17]. One major approach to EGFR inhibition is the use of small-molecule inhibitors of intracellular tyrosine kinase domain which block the extracellular domain of the receptor. Gefitinib and erlotinib are orally administered EGFR-tyrosine kinase inhibitors, which compete with ATP for binding to the tyrosine-kinase domain.

EGFR-TKIs Resistant mutations

EGFR overexpression has been associated with a number of cancers, including lung cancer. Its constant activation was due to the involvement of somatic mutations. Most patients with NSCLC were reported to have tumour associated EGFR mutations [18, 19]. These mutations occur within EGFR exons 18–21, which encodes a portion of the EGFR kinase domain (**Figure 2**). Exon 19 deletions or exon 21 L858R point mutations are the most frequently recorded in patients with NSCLC [21, 22]. Resistance to kinase inhibitors targeting epidermal growth factor receptor (EGFR) tyrosine kinase was reported in patients with non-small cell lung cancer; documented resistance cases were associated with primary resistance mutations such as exon 20 insertions which comprise approximately 4–9.2% of all *EGFR*-mutated lung tumors [23, 24]. Most EGFR exon 20 insertions occur in between amino acids 767 to 774 of exon 20, within the loop that follows the C-helix of the kinase domain of EGFR [25]. Decreased sensitivity to reversible and irreversible EGFR-TKIs [26-29], and to mutant-selective covalent EGFR-TKIs WZ4002 [30] and CO-1686 [31] were reported to be associated with resistant mutations, EGFR exon 20 insertion mutants, outside of A763_Y764insFQEA. Also, patients with tumors harboring EGFR exon 20 insertion mutations involving amino acids A767, S768, D770, P772 and H773 were reported to display lack of response when treated with gefitinib or erlotinib [32, 33]. In retrospective and prospective analyses of patients with NSCLCs harboring typical EGFR exon 20 insertions, most displayed progressive disease in the course of treatment with gefitinib or erlotinib or afatinib [34]. It is not worthy that N771GY and A767-V769dup, which are novel somatic insertion mutations in exon 20, and S768N, a missense mutation, were all identified in the African American cohort [35, 36]. In East Asian patients, S768I, a somatic EGFR mutation, was reported with evidence, suggesting a potential role in EGFR TKI resistance [37, 38]. The *EGFR* mutational status seems also to vary between the primary lung tumor and the corresponding metastases. Often, the *EGFR* mutations would be present in the primary lung tumor but appear to be absent in the metastases. According to several studies, the discordance rate of *EGFR* mutations ranged between 16.2% to 32.5% [39, 40]. Another most common cause of TKI resistance is the development of a second EGFR mutation known as T790M. The substitution of threonine with methionine at amino acid position 790 (T790M), as the second mutation in EGFR, is the most common resistance mechanism. The EGFR T790M mutation on exon 20 occurs in 50% to 60% of patients initially diagnosed with an EGFR-activating or – sensitizing mutation (either an exon 19 deletion or exon 21 L858R mutation) who experience disease progression with a first-line EGFR TKI [41, 42]. Other aberrations that may give rise to EGFR TKI resistance include PIK3CA mutations, EMT or MET amplification, or conversion to small cell lung cancer histology [43, 44].

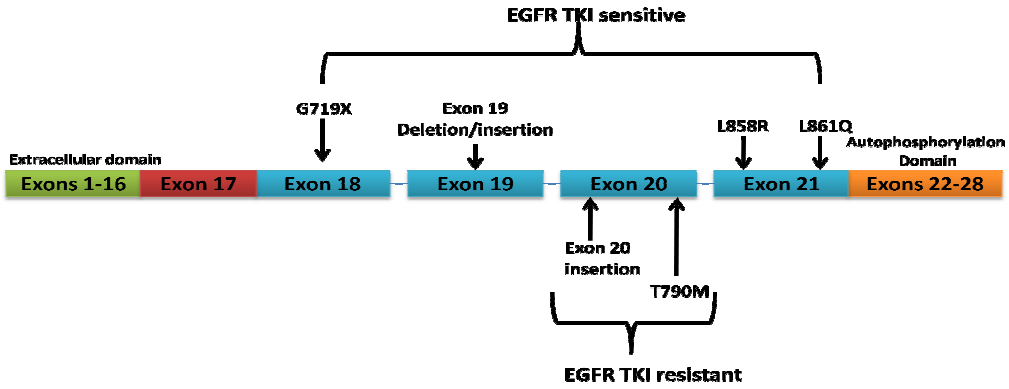

Figure 2:EGFR mutations. Exons 18–21 of the EGFR kinase domain are depicted. Mutations above the schematic are associated with sensitivity to EGFR TKIs. Mutations listed below the schematic are associated with EGFR TKI resistance. *Adapted from://www.mycancergenome.org*

Adverse events associated with EGFR-TKI Therapy

Although much less toxic than the treatments they replaced, EGFR-TKIs are generally better tolerated than cytotoxic chemotherapy. In randomized phase III clinical trials, many patients with advanced NSCLC harboring EGFR mutations that have been treated with EGFR-TKIs as first-line treatment were reported to develop side effects that adversely affect their life [45, 46]. The most common adverse reactions with EGFR-

TKI are rash-like events that erupts most often on the face but can also be seen on the chest, back, trunk, and limbs, and it was observed in IPASS (66.2%), First SIGNAL (72.4%), WJTOG 3405 (76%), and NEJ002 (71%) studies in patients treated with gefitinib, in OPTIMAL (73%), EURTAC (80%) studies in patients treated with erlotinib and in LUX-Lung 3 (89.1%), LUX-Lung 6 (80.8%) studies in patients treated with afatinib [47-51]. In the BR.21 trial, grade 3/4 rash was reported to occurr in 9% patients with a median time to onset of 8 days [52].

Diarrhea is another common class effect of these drugs. It can be seen at any time during treatment with EGFR inhibitors. Severe diarrhea occurred in about 3% to 6% of the patients taking erlotinib or gefitinib in phase III trials. Other less common side effects can be nausea and vomiting, anorexia, and stomatitis.

Rare but statistically significant occurrences of interstitial lung disease (ILD) have been reported in randomized Phase III clinical trials. In studies of gefitinib, ILD occurred in 0.3% to 1% of the US population and in about 2% of Japanese patients [53]. ILD rates in the BR.21 trial erlotinib trial were less than 1% [54].

VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS

Vascular endothelial growth factor (VEGF), a mitogen specific for vascular endothelial cells, plays a key role in angiogenesis. VEGF-related angiogenic signal is mediated by kinase domain receptor (KDR) and Fms-like tyrosine kinase (Flt-1), which have intracellular tyrosine kinase activity [55]. Multiple tyrosine kinase receptors which appear to have important roles in the generation of new vessels from pre-existing ones for rapid tumor growth and, as such, represent reasonable targets for chemotherapy strategy. Multi-targeted tyrosine kinase inhibitors (cediranib, motesanib, sorafenib, sunitinib, vandetanib, nintedanib, pazopanib, linifanib, axitinib, etc) have been studied in many randomized controlled trials for treatment of advanced non-small cell lung cancer (NSCLC) [56]. A meta-analysis of randomized controlled trials compare the efficacy and toxicity of chemotherapy plus multi-targeted TKI with chemotherapy alone in patients with advanced NSCLC; therapy consisting of chemotherapy plus multi-targeted TKI was reported by Xiao *et al.* to have specific advantages over chemotherapy alone in terms of PFS and ORR [57]. The key tyrosine kinase target that has generated the most interest through targeting crucial steps of angiogenesis is VEGFR. FDA approved and those under investigation are orally active small molecule inhibitors which target VEGF family of tyrosine kinases and a wide spectrum of other tyrosine kinase receptors.

Challenges Associated with VEGFR-TKIs Therapy

Survival of endothelial cells is highly related to growth factor signaling under normal physiological conditions. Inhibitors of angiogenesis via inhibition of VEGFR related tyrosine kinase are capable of affecting signaling pathways in endothelial cells and thus might elicit toxicities as a result of decreased endothelial cell renewal capacity [58]. A meta-analysis of 10 randomized controlled trials showed that the use of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors was associated with an increased risk of fatal adverse events. Roberto, *et al*. [59] reported the incidence and risk of hepatic toxicity in patients receiving VEGFR-TKIs through a large up-to-date meta-analysis of available clinical trials. It is known that, one kinase is able to activate several downstream signaling pathways. By inhibition of a kinase with a tyrosine kinase inhibitor, downstream signaling pathways can be deactivated. This might perturb specific biological outcomes which are not intended to adjust. It has been shown that specific kinases are involved in the normal physiology of certain organs such as kidneys and the thyroid gland. It has been suggested that specific toxicities, like nephrotic syndrome and fatigue, might be related to interference of these inhibitors with the normal function of these organs [60, 61]. Besides the vascular effects observed with inhibition of the vascular endothelial growth factor (VEGF) pathway (i.e., hypertension and hemorrhage), direct functional effects on the heart have been observed for several small molecule TKIs; sorafenib has been associated with cardiac ischemic/infarct events in as many as 2.9% of patients [62]. Effects on cardiac function have also been associated with sunitinib which has been associated with increases in patients with left ventricular ejection fractions below the lower limit of normal leading to congestive heart failure in some cases [63].

Summary

A number of studies of the molecular mechanisms of lung cancer has led to the description and understanding of several genetic abnormalities. Among these, the identification of a number of potentially targetable driver mutations in growth related protein kinases, especially tyrosine kinases in lung cancer and have led to the discovery of several potential molecular targets for therapeutic design, such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) [64, 65]. The development of effective chemotherapeutics which target growth factor receptor tyrosine kinases in non-small cell lung cancer has significantly improves patients' treatment outcome. However, resistance to tyrosine kinase inhibitors in NSCLC is an increasingly recognized issue. Future priorities for the development of growth factor receptor tyrosine kinase agents in NSCLC include the development of drugs that effectively inhibit a network of growth factor induced signaling pathways. Also, further biological studies are required to better understand the pathogenesis of lung cancer, especially non-small cell lung cancer, in order to improve treatment response.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgement

I would like to thank Prof. YU Liu and Prof. ZHOU. G (Chinese academy of science) for providing critical comments, members of the laboratory of Prof. YU Liu (China Pharmaceutical University, Nanjing, China PRC) and members of the "Centre de Traitement du Cancer" (Hopital National de Niamey, Niger) for their involvement in providing supportive ideas as well.

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Cite this article as: Lawaly Maman Manzo, Moudirat Lawaly, Lui YU. Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-small cell lung cancer **Indian J. Pharm. Biol. Res.2015; 3(2):81-87.**

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