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Review Article

Understanding The Role of Molecular Targeted Therapeutic Drugs In Non-Small Cell Lung Cancer (NSCLC): A Narrative Review

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ABSTRACT

Worldwide the second most common cancer is lung cancer with tobacco as the main reason for the disease. Lung cancer is chiefly classified into small cell lung cancer and non-small cell lung cancer. Various genes that cause tumorigenesis in non-small cell lung cancer are linked to multiple pathways like ALK, MET, EGFR, and RET. Genomic profiling and mutational analysis in recent years have progressed the field of genetics of lung cancer substantially. In this present review, we converse about the various targeted therapeutic drugs and their advancement in treatment of non-small cell lung cancer (NSCLC). The present review scrutinize the existing documentation in the literature related to the targeted therapies of non-small cell lung cancer (NSCLC). English language articles were searched in various databases such as Pubmed, Scopus, Science direct and Google scholar. The keyword used for searching are “non-small cell lung cancer”, “Targeted therapy”, “Therapeutic drugs”.

INTRODUCTION

One of the principal reasons for cancer-related mortality is lung cancer. Worldwide more than one million deaths occur because of lung cancer. Death from lung cancer and other respiratory system cancer would surpass the number of deaths from cancers of the colon, breast, pancreas, and prostate combined. About 80% of all cases of lung cancer are NSCLC (Non-small cell lung cancer) and are

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actively associated with smoking habits. Small cell lung cancer is solely diagnosed in smokers.[1,2,3]

Lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD) are the most common subtypes of non-small cell lung cancer.[4] Smoking tobacco is precisely linked with non-small cell lung cancer and more than 50 carcinogens are found in the smoke of tobacco.[5]

Tobacco regulation is expected to be an advantageous and useful method to decrease the mortality and incidence of cancer of the lung. Various carcinogenic factors like genetic mutations, bad lifestyle, and a history of cancer in the family also contribute to cancer of the lung. Other than the prevention of cancer, screening of lung cancer is also important in detection in early-stage patients, in which low-dose computed tomographic screening decreases lung cancer mortality.[6]

During the last few decades, much development has been done in various therapeutic strategies for advanced non-small cell lung cancer specifically in the development of immunotherapy and targeted therapy. Various considerable small molecular tyrosine kinase inhibitors (TKIs), which target fusions in ROS1(ROS proto-oncogene 1), EGFR (epidermal growth factor receptor) mutation, MET (mesenchymal-epithelial transition) exon 14 skipping, rearrangements in ALK (anaplastic lymphoma kinase), NTRK (neurotrophic tyrosine receptor kinase)1/2/3 gene fusion, and RET (rearranged during transfection) rearrangement and BRAF (v-Raf murine sarcoma viral oncogene homolog B) V600E have been recognized by the U.S food and drug administration for the treatment and therapy of driven gene mutation-positive non-small cell lung cancer.

As a result of comprehensive genomic profiling, different genetic aberrances in non-small cell lung cancer, like an amplification of HERS-2 (human epidermal growth factor-2), mutations in KRAS (Kirsten rat sarcoma), and different genotypes of driver genes thought to be highly targetable and researched in various preclinical and clinical trials. Monoclonal antibodies (mAbs) that target programmed cell death ligand-1(PD-L1), programmed cell death-1(PD-1), and cytotoxic T-lymphocytes associated antigen-4 (CTLA-4) immune checkpoints have been accepted for the treatment of various type cancers including non-small cell lung cancer. There are five immune checkpoint inhibitors that are approved by the food and drug administration including ipilimumab (anti-CTLA-4 antibody), atezolizumab and durvalumab (anti-PD-L1 antibodies), and nivolumab and pembrolizumab (anti-PD1 antibodies).[7]

Various molecular testing for NSCLC

Non-small cell lung cancer is a molecularly heterogeneous disease, that makes initial recognition of tumor genotype analytical. ALK, EGFR, and ROS1 at first approved as three targetable oncogenic drivers, which are essentially tested if the tissue is restricted for NGS (next-generation sequencing) panel.NCCN advised that all patients must be screened for ALK, BRAF, EGFR, MET, KRAS, PD-L1, and RET expression.[8] The most traditional way to determine genomic mutations is DNA sequencing which needs comparably enriched tumor cells. Oncogenic fusion mutation can be examined by PCR or FISH (fluorescence in situ hybridization). NGS is now considered a typical molecular testing method and has adequate potential to evaluate the data from DNA and RNA.[9,10] RNA NGS is also efficient to determine the fusion partners of ROS1, NTRK, ALK, and RET.[11-14]To identify circulating tumor DNA, liquid biopsies are used.[15] Immunohistochemistry (IHC) is an alternate method for testing, mainly ROS1, ALK and NTRK.[16,17]

VARIOUS TARGETED THERAPY FOR NSCLC

Patients with progressive non-small cell lung cancer benefit a lot from the advancement of targeted therapy. Approximately more than 65% of patients with progressive non-small cell lung cancer have a probable targetable genomic alteration. Targeted therapy is now recognized as first-line treatment for selected non-small cell lung cancer patients which includes inhibitors for BRAF, MET, EGFR, ROS1, RET, ALK and NTRK1/2/3.[18]

EGFR (Epidermal Growth Factor Receptor)

The EGFR (epidermal growth factor receptor or ErbB1 or HER1) is part of a family of receptor tyrosine kinases that can provoke a broad array of signaling pathways that result in cell growth, survival, and proliferation. These signaling pathways include the PI3K-AKT-mTOR pathways and RAS-RAF-MEK-ERK or MAPK pathway.[19,20]

EGFR activation occurs by three mechanisms. These are enhanced ligand production by malignant cells; increased expression of EGFR on malignant cells and activating mutations of EGFR within malignant cells.[21,22] In humans, there are 58 RTKs (receptor tyrosine kinases).EGFR (epidermal growth factor receptor) is one of the first receptor tyrosine kinases marked as an anticancer target and causes meaningful development in survival in patients of non-small cell lung cancer.[23]

Expression of EGFR is normally seen on the surface of epithelial cells and manages cell growth, invasion, survival, and angiogenesis.[24] EGFR mutation in patients of non-small cell lung cancer takes place in nearly 40% of Asian patients and 10% of non-Asian patients.[25,26]

The most frequent activating mutations of EGFR in non-small cell lung cancer consists of exon 19 deletions and point mutation on exon 21, which is accountable for oral tyrosine kinase inhibitor (TKIs) targeting EGFR.[27] There are three generations of EGFR TKIs used in clinical function. The first-generation EGFR TKIs reversibly attach to EGFR and aggressively restrict the binding of ATP to the tyrosine kinase domain. The first-generation EGFR TKIs include erlotinib, gefitinib, and icotinib.[28] The second-generation EGFR TKIs attach to the ATP binding domain of EGFR irreversibly. The second-generation EGFR TKIs include afatinib and dacomitinib and they are irreversible ERBB-family inhibitors. Depending on the results of three clinical trials, LUX-Lung 6, LUX-Lung 3, LUX-Lung 2, afatinib demonstrate extended PFS of almost 1 year in patients having progressive non-small cell lung cancer with EGFR mutations.[29,30,31]

Almost all the patients who have taken first or second-generation EGFR TKIs treatment ultimately attained drug resistance which results in disease progression.[32] Osimertinib is a third-generation EGFR TKI. They irreversibly and selectively target the T790 mutation and original EGFR-sensitizing mutations. The most common second mutation is T790M which causes drug resistance, which is attributed to threonine-tomethionine substitution in exon 20.[33,34] The third-generation EGFR TKIs include olmutinib (HM61713), avitinib, rociletinib, nazartinib (EGF816), PF-06747775.[35-39] Osimertinib crosses the blood-brain barrier and enters the central nervous system and destroy the tumor cells. Currently, furmonertinib was approved by NMPA and is third generation EGFR TKI.[40]

ALK (Anaplastic lymphoma kinase)

Anaplastic lymphoma kinase or ALK is an RTK commonly expressed in various human tissues like the small intestine, brain, and testis.[41] ALK fusion proteins are mostly found as an oncogenic driver in different malignancies. ALK rearrangements in non-small cell lung carcinoma have been observed in 2007 by the early discovery of a fusion gene that consists of parts of the EML4 gene (echinoderm

microtubule-associated protein-like 4) and ALK gene. More than 20 variants of ELM4-ALK fusion were recognized.[42-44]

There are five ALK TKIs that have been recognized as targeted therapy for progressive non-small cell lung cancer patients who are proven to have ALK arrangements. These are alectinib, crizotinib, brigatinib, ceritinib, and loralatinib. Crizotinib is first generation ALK TKI that targets ROS1, ALK, and MET.[45] Ceritinib and alectinib are second-generation ALK TKIs that are approved to use in those cases of non-small cell lung cancer which fail in or tolerate crizotinib therapy. Ceritinib could adequately restrict certain ALK alteration patterns like G1269A, S1206Y, and L1196M mutations. On the other hand, they are not able to conquer two crizotinib resistant ALK mutations i.e. F1174C and G1202R.[44,46,47]

Earlier, Brigatinib was accepted for second-line treatment in patients of progressive ALK-positive non-small cell lung cancer. Brigatinib targets both ALK and EGFR.[48,49] Currently in march 2021, lorlatinib, earlier second-line ALK TKI, has been recognized as a first-line treatment for progressive ALK-positive non-small cell lung cancer patients. Lorlatinib target numerous RTKs consisting of ROS1 and ALK.[50] Lorlatinib is a third-generation ALK TKI that has adequate potential to overcome ROS1 and ALK resistance mutations like G1202R and I1171T. Lorlatinib showed various advantages which include less drug resistance and penetration into the central nervous system on comparing with former-generation ALK TKIs.[51,52]

ROS1

ROS1 is an oncogenic RTK of the insulin receptor family. They are encoded on chromosome 6q22 by the ROS1 gene. The oncogenic consequences of ROS1 depend on basic phosphorylation and are stimulated by fusions with partner genes like FIG (fused in glioblastoma), CD74, and SLC34A2 (so lute carrier family 34 member 2).[53-56] Crizotnib was accepted for the treatment of ALK-positive non-small cell lung cancer. Crizotinib has targeted agents used in ROS1-positive progressive non-small cell lung cancer. At the same time, Entrectinib has been accepted for the treatment of progressive ROS1-positive non-small cell lung cancer.[57,58]

BRAF

In 3-8 % of non-small cell lung cancer, BRAF mutations have been seen.[59,60] Single point mutation at exon 15 is the most common alteration of BRAF mutations in which glutamate replaces the valine (V600E, Val600Glu). The threonine/serine protein kinase, which is linked in MAPK/ERK signaling pathway, is encoded by the BRAF gene. Mutation in V600E results in uncontrolled activation of BRAF, which further causes abnormal cell proliferation.[61]

KRAS (Kirsten rat sarcoma 2 viral oncogene homolog)

KRAS is an oncogene that is part of the RAS GTPase family. They assist in the regulation of various important cellular pathways encompassing PI3K/AKT and RAF/MEK/ERK.[62]KRAS mutations are frequently seen in non-small cell lung cancer which accounts for 25% of adenocarcinomas. The genomic aberrations of KRAS result in constant stimulation of KRAS.[63,64]

RET

On the cell surface, RET encodes a tyrosine kinase receptor. It participates in various important signaling pathways which comprise JAK/STAT, MAPK, PKC, PI3K, and PKA pathways.[65] In 1-2 % of non-small cell lung cancer RET fusion or RET arrangements have been identified. The most common fusion partner of RET is intron 15 of KIF5B.[66,67]

MET (mesenchymal-epithelial transition factor)

The MET gene encodes hepatocyte growth factor receptor and the phosphorylation of this results in the stimulation of various cellular signaling pathways which includes PI3K, MAPK, and

STAT. The amplification of MET is generally linked with EGFR TKIs resistance.[68]Most common pattern of MET mutations is skipping of MET exon 14, which results in constant stimulation of MET protein.[69] Crizotinib was recognized for second-line treatment of MET exon 14 skipping positive in patients of non-small cell lung cancer. Tepotinib and capmatinib are MET TKIs used in the treatment of MET exon 14 skipping mutation-positive in progressive non-small cell lung cancer. Various approaches to prevent MET.HGFR-mediated growth is in progress which includes anti-HGFR mAb, HGF antagonists, anti-MET mAb and MET TKIs like cabozantinib (XL184), tivantinib (ARQ197), and crizotinib.[70,71]

NTRK

Tropomyosin receptor kinases A, B, and C are encoded by NTRK (Neurotrophic tropomyosin-related kinases) genes 1,2, and 3. 1-2% of non-small cell lung cancer patients show NTRK fusion. Entrectinib, larotrectinib, and repotrectinib were recognized for the treatment of NTRK gene fusion-positive solid tumor which includes non-small cell lung cancer.[72,73]

HER2 Human epidermal growth factor 2 (HER2/ErbB2/neu)

HER2 (ERBB2), HER3, and HER4 are part of the ERBB RTK family.[74] Overexpression of HER2 is relatively seen in 10% of lung cancer. Also, amplification of HER2 is seen in 30% of lung cancer.[75,76] The common mutations seen in HER2 take place in exon 20 by the inclusion of DNA bases. Various targeted agents like antibody-drug conjugates (ADCs), antibodies (transtuzumab and pertuzumab), and small molecular TKIs (dacomitinib, poziotinib, lapatinib, pyrotinib) have been examined in various clinical trials.[77,78]Antibody-drug conjugates demonstrate most promising therapeutic effects for HER2 mutation-positive in patients of non-small cell lung cancer.[79]

VEGF/VEGFR

In addition to targeting genomic alterations, the formation of inhibition tumor vasculature by targeting the angiogenic determinants is also a hopeful and characteristic anticancer approach.[80]Microvessels having high density are linked with poor prognosis and metastasis of non-small cell lung cancer. VEGF (vascular endothelial growth factor) and the communication with its receptors are found to be most effective in controlling angiogenesis and are also capable to intensify the vascular permeability.[81,82]

Suppression of tumor angiogenesis is presumed as an encouraging therapeutic approach. The anti-angiogenic treatment for non-small cell lung cancer consists of small molecule TKIs, mAbs, and recombinant human endostatin. Ramucirumab and Bevacizumab are two mAbs accepted for the treatment of non-small cell lung cancer. Bevacizumab is the first antiangiogenic drug that prohibits angiogenesis by neutralizing all isoforms of VEGF.[83] Bevacizumab in consolidation with paclitaxel and carboplatin was accepted as the first-line treatment of progressive non-squamous non-small cell lung cancer.[84] Ramucirumab, a monoclonal antibody, attaches to the extracellular VEGF-binding domain of VEGFR-2, which results in the suppression of angiogenesis.[85,86]

TKIs targeting platelet-derived growth factor/receptor (PDGF/PDGFR), c-Kit, VEGF/VEGFR and fibroblast growth factor/ receptor (FGF/FGFR) illustrate the consequence on inhibition angiogenesis including sunitinib, nintedanib, sorafenib, vandetanib and anlotinib.[87-90] Anlotinib suppresses a wide spectrum of targets which includes FGFR1-4, c-Kit, VEGFR2/3, PDGFR α/β, and Ret, which is expected to have extreme effects on anti-angiogenesis.[91]

CONCLUSION

In the last few decades, meaningful advancement in molecular pathology occurs and it allowed us to explain the basic pathology and considerable

heterogeneity of non-small cell lung cancer. Numerous signaling pathways have now been recognized as well as particular oncogenic driver mutations that result in malignant transformations. In current decades, target therapy and immunotherapy have made a notable significant addition to the modernized management of lung cancer. Furthermore, genetic testing and biomarker analysis helps in the special management and treatment of numerous forms of lung cancer.

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