Tyrosine kinase inhibitors (TKI) used in the treatment of non-small cell lung cancer (NSCLC) based on specific genetic alterations

Abstract

This review aims to describe the main TKI inhibitor therapeutic agents used in targeted therapy of non-small cell lung cancer (NSCLC).Thus, we described: Osimertinib, Erlotinib, Gefitinib, Afatinib, Dacomitinib, Alectinib, Brigatinib, Lorlatinib, Crizotinib.We also made some remarks on Entrectinib because among the molecular determinations approved for reimbursement is the determination of NTRK fusion for which Entrectinib is recommended. We also briefly presented the side effects of these compounds that sometimes limit their use.

Key words: TKI, Non small cell lung cancer, target therapy

Background

Lung cancer is the leading cause of cancer deaths worldwide.Lung cancer causes more deaths than blood, colorectal, prostate, and brain cancers combined.In 2021, an estimated 235,760 new cases of lung cancer were diagnosed in the United States.The number of deaths was estimated at over 131,880.Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for more than two-thirds of cases.Most patients (84%) have advanced disease at the time of diagnosis.Identification of genetic changes that can be driver mutations: EGFR, ALK, PI3K/AKT/mTOR, RAS-MAPK, RET, MET, BRAF, and NTRK/ROS1 guides appropriate treatment.The approval and adoption of therapeutic providers that target these genetic alterations has led to a 35% decrease in mortality among men with NSCLC diagnosed in 2001 to 26% in 2014. Similar rates have been found among women with NSCLC.Despite these new therapeutic

agents for patients with advanced NSCLC, the development of resistance and disease progression occurs in the majority of patients.Patients develop resistance to these agents. The emergence of resistance to therapeutic agents has led to research into drugs that can overcome these resistance mechanisms.Next-generation sequencing, which can be performed on tumor tissue obtained by biopsy or on circulating tumor DNA (ctDNA) in the blood, is now the standard of care for all patients with advanced NSCLC.This identifies actionable mutations and resistance mechanisms (1).

In 2024, several targeted therapeutic agents are used in the treatment of NSCLC based on genetic alterations detected:

1. EGFR Mutations:
    - Osimertinib
    - Erlotinib
    - Gefitinib
    - Afatinib
    - Dacomitinib
2. ALK Rearrangements:
    - Alectinib (ALECENSA, Hoffmann-La Roche, Inc./Genentech, Inc.) for treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC),
    - Brigatinib
    - Lorlatinib
    - Crizotinib
3. ROS1 Rearrangements:
    - Crizotinib
    - Entrectinib

Osimertinib is the first third-generation E GRF-TKI approved for the treatment of NSCLC. An important study that defined the role of Osimertinib in the treatment of NSCLC was the AURA3 study. In this study, progression-free survival (PFS) was significantly prolonged in the Osimertinib arm and the response rate was also significantly improved compared to platinum-pemetrexed chemotherapy in patients with centrally confirmed EGFR T790M advanced NSCLC and progression on first-line EGFR-TKI therapy. Mature OS data were encouraging(2).

Another approval for Osimertinib was in the adjuvant setting, as on December 18, 2020, the Food and Drug Administration approved Osimertinib for the adjuvant treatment of patients with NSCLC whose tumors harbor EGFR exon 19 deletions or exon 21 L858R mutations. Detection of the EGFR mutation was done using FDA-approved tests (3).

Osimertinib is currently used in first-line treatment of NSCLC (On February 16, 2024, the Food and Drug Administration approved osimertinib with platinum-based chemotherapy for patients with locally advanced or metastatic NSCLC who have EGFR exon 19 deletions or exon 21 L858R mutations. On February 16, 2024, the FDA approved Osimertinib in combination with platinum-based chemotherapy for patients with locally advanced or metastatic NSCLC (4).

The main side effects of osimertinib are: anxiety, cough, dizziness, fainting, blurred vision, tachycardia, strong or uneven heartbeats, pain in the chest, groin, or legs, especially in the calves, pain, redness, or swelling of the arm or leg.You may also experience: slurred speech, sudden loss of coordination, sudden, severe headache, weakness or numbness in the arm or leg, and difficulty breathing (5).

LAZERTINIB

Lazertinib is a third-generation oral epidermal growth factor receptor (EGFR) inhibitor (TKI) that has been validated for the treatment of NSCLC. It is an irreversible EGFR-TKI that crosses the blood-brain barrier, activates the EGFR Ex19del and L858R mutations, and also acts on the T790M mutation but not on the wild-type EGFR mutation. In January 2021, lazertinib received approval for the treatment of patients with locally advanced or metastatic NSCLC positive for the EGFR T790M mutation in the second line for patients who have previously received, in the first line, therapy with another EGFR-TKI (6).

On August 19, 2024, the FDA, following the results of the MARIPOSA study, approved lazertinib in combination with amivantamab for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R mutations, following an FDA-approved laboratory test (7). The MARIPOSA study was presented at ESMO 2023. This study is for patients with NSCLC with classic EGFR mutations without prior therapy with advanced or metastatic disease. In this study, patients received the bispecific antibody amivantamab, which is an EGFR and MET antibody, in combination with lazertinib, a third-generation EGFR – TKI. The comparator was osimertinib and there was also a lazertinibmonotherapy arm. And, the primary endpoint was progression-free survival by blinded independent review, was reached (8).

The main side effects of Lazertinib are: allergic reaction; skin reactions: raised, acne-like bumps, skin rash, itching, or dryness. Visual problems--eye pain or redness, itching, dry or watery eyes, increased sensitivity to light. Major side effects could be stoke, blood clot in the lung etc. Common sife effects could be: infected skin around the nail, diarrhea or constipation, bleeding, mouth sores, nausea, loss of appetite (9)

GEFITINIB, ERLOTINIB AND AFATINIB

The first 2 drugs are first-generation EGFR TKIs and the last (Afatinib) is a second-generation EGFR TKI. These drugs have been used for a long time to treat advanced NSCLC, with proven efficacy. Zuyao Yang and colleagues performed a meta-analysis of studies using these compounds. This meta-analysis demonstrated that Gefitinib and Erlotinib influenced progression-free survival in the some percent and have the some results for overall response rate and disease control rate, which did not vary significantly with ethnicity, line of treatment and brain metastases, metastases at baseline. The toxicity of these drugs has some peculiarities as follows: Gefitinib was associated with grade 3/4 liver dysfunction with a higher frequency leading to treatment discontinuation. Specific adverse events, such as rash and diarrhea, were common with both Gefitinib and Erlotinib. There was no strong evidence that Afatinib was more effective than Gefitinib or Erlotinib in the first-line treatment of EGFR-mutant NSCLC. Afatinib,

in a meta-analysis, was more effective than Erlotinib in the second-line treatment of patients with advanced squamous cell carcinoma. Regarding the toxicity profile, Afatinib caused a rate of grade 3/4 adverse events comparable to that of erlotinib, but higher than that of gefitinib. In the study by Yang, James Chih-Hsin et al., Afatinib has clinical activity in NSCLC against more common EGFR mutations. It also has better activity against some exon 20 insertions (9,10).

DACOMITINIB

Dacomitinib is a selective and irreversible inhibitor of EGFR. In one study, approximately 10% of patients with NSCLC harboring EGFR mutations presented as uncommon mutations. This study aimed to explore the efficacy and safety of dacomitinib, a second-generation EGFR-TKI, in treating advanced, uncommon NSCLC harboring EGFR mutations. Major treatment-emergent adverse events (TREAEs) included rash (87.5%), paronychia (62.5%), oral ulcers (50.0%), and diarrhea (50.0%), none of which were ≥ Grade 3 ETRs (11).

ALECTINIB

Alectinib has been approved by the FDA for the treatment of patients with anaplastic lymphoma kinase-positive rearrangement (ALK-positive) metastatic NSCLC. The approval was based on data from the ALEX trial (NCT02075840), a randomized, phase 3, multicenter, open-label study in 303 patients with ALK-positive NSCLC who had not received any prior systemic therapy for metastatic disease. ALK rearrangement was determined by the VENTANA ALK CDx Assay (D5F3) performed at a central laboratory. Patients were randomized 1:1 to receive oral alectinib twice daily (n=152) or oral crizotinib twice daily (n=151). The ALEX trial demonstrated an improvement in progression-free survival (PFS), as assessed by blinded IRC (BIRC), with a hazard ratio (HR) of 0.53 (95% CI: 0.38, 0.73; p0.0001). Important adverse reactions that led to discontinuation of alectinib in 1% or more of patients were: renal failure, hyperbilirubinemia, increased alanine aminotransferase, and increased aspartate aminotransferase (12)

BRIGATINIB

Brigatinib was approved by the FDA on May 22, 2020, for patients with NSCLC and anaplastic lymphoma kinase rearrangement. Brigatinib was administered for metastatic disease. ALK

detection was also performed using an FDA-approved assay. Brigatinib was shown to be effective for the indicated indication investigated in the ALTA 1L study (NCT02737501), a multicenter, open-label, randomized (1:1) trial. Adult patients with ALK-positive advanced NSCLC who had not previously received ALK-targeted therapy were enrolled in the study. The study enrolled patients who had an ALK rearrangement based on a local standard diagnostic test. The primary efficacy outcome was progression-free survival (PFS). Thus, the median estimated PFS for patients treated with brigatinib was 24 months (95% CI: 18.5, NE) compared with 11 months (95% CI: 9.2, 12.9) for those treated with crizotinib (HR 0.49; 95% CI: 0.35, 0.68).); p<.0001). The confirmed ORR was 74% (95% CI: 66, 81) and 62% (95% CI: 53, 70), respectively (13). Brigatinib has several side effects, most of which are similar to other ALK inhibitors: Interstitial lung disease/pneumonitis, Hypertension, Bradycardia, Visual disturbances, Hepatoxicity, Hyperglycemia (14).

LORLATINIB

Lorlatinib is a third-generation ALK- TKI and ROS1 inhibitorthat penetrates the brain. It also has broad coverage of ALK resistance mutations. Lorlatinib has an effect on overall survival (OS) in NSCLC. The long-term safety of lorlatinib has been demonstrated in patients with advanced ALK-positive NSCLC. These data come from the final analyses of a pivotal phase 2 study. In this phase 2 study, after a minimum follow-up of 5 years, the final overall assessments confirmed substantial activity of Lorlatinib: prolongation of OS, and overall important findings regarding the safety of Lorlatinib in patients with metastatic NSCLC in both previously untreated and previously treated ALK-positive patients (15). The most common side effects of lorlatinib are: edema, peripheral neuropathy, cognitive effects, dyspnea, cough, fatigue, weight gain, arthralgia, mood effects, and diarrhea (16).

CRIZOTINIB

Crizotinib is the first inhibitor of the anaplastic lymphoma kinase rearrangement (ALK) used in the treatment of ALK and/or ROS1-positive metastatic NSCLC, as well as ALK-positive anaplastic large cell lymphoma (ALCL) and inflammatory myofibroblastic tumor (IMT). By targeting the echinoderm microtubule-associated protein 4 (EML4)-ALK fusion, crizotinib offers

good efficacy in treating NSCLC in patients with this type of rearrangement. Crizotinib was the first drug in its class to be used to treat ALK-positive tumors. Currently, new generations of ALK-TKIs (second and third generation) have overcome many of the pharmacodynamic and genetic resistance mechanisms to which crizotinib is prone. Crizotinib was approved by the FDA in 2011. The FDA has also approved tests to detect ALK and ROS1 rearrangements (17). The main adverse reactions are: respiratory problems associated with pneumonitis/ILD o dizziness, fainting, chest discomfort or irregular heartbeat associated with bradycardia, QT prolongation and heart failure o liver blood test abnormalities associated with hepatotoxicity o visual changes, including guidance for assessing visual symptoms in the pediatric population o Stomach upset associated with gastrointestinal perforation (18)

ENTRECTINIB

NTRK fusions result in constitutively active oncogenic TRK proteins responsible for approximately 0.2% of non-small cell lung cancer (NSCLC) cases. Approximately 40% of patients with advanced NSCLC develop CNS metastases; therefore, treatments with intracranial (IC) efficacy are required. Entrectinib has continued to demonstrate profound and durable systemic and IC responses in patients with NTRK-fp NSCLC (19). Entrectinib has demonstrated substantial systemic and intracranial efficacy in ROS1 TKI-naive patients with fusion-positive ROS1 NSCLC. The overall efficacy and intracranial efficacy observed with entrectinib when patients had CNS progression on prior crizotinib treatment were modest. Based on these data, physicians should carefully consider the most appropriate TKI treatment sequence for each patient. To ensure maximum efficacy, entrectinib should be considered a first-line treatment for patients with ROS1 fusion-positive NSCLC (13). The most common adverse events were dysgeusia, fatigue, dizziness, constipation, diarrhea, nausea, weight gain, paresthesia, increased creatinine, myalgia, peripheral edema, vomiting, arthralgia, anemia, and increased AST (20,21).

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