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Review Article

Oncology Section

A Review on Newer Tyrosine Kinase Inhibitors and their Uses

NITHU M KUMAR[1], MEENU MATHEW[2], KN ANILA[3], S PRIYANKA[4]

ABSTRACT

Tyrosine Kinase Inhibitors (TKI) can reversibly or irreversibly block the signaling pathway occurring in the extracellular part of the receptor by inhibiting Tyrosine Kinase (TK) phosphorylation. This review included the drugs that were newly marketed or drugs with newer approved uses after 2015, such as Gefitinib, Osimertinib, Crizotinib, Alectinib, Ibrutinib, Cabozantinib. Brigatinib and Lorlatinib are investigational drugs that have not been approved and have shown promising results in trials for the treatment of Anaplastic Lymphoma Kinase (ALK) positive metastatic Non Small Cell Lung Carcinoma (NSCLC). Gefitinib, Osimertinib, Crizotinib, Alectinib were approved for treating NSCLC. Cabozantinib and Lenvatinib were approved for treating renal cell carcinoma and thyroid carcinoma. Ibrutinib was approved for treatment of Chronic Lymphocytic Leukaemia, Small Lymphocytic Lymphoma, Waldenström macroglobulinemia, previously treated Mantle cell lymphoma and relapsed or refractory Marginal zone lymphoma.

TKI have promising efficacy in treating a wide range of oncologic diseases. Hand-foot-skin reaction are the most common side effect of drugs in this category, however, TKI are found to have relatively fewer side effects compared to other anti cancer drugs.

Keywords: Anaplastic lymphoma kinase, Bruton's tyrosine kinase inhibitor, Epidermal growth factor receptor inhibitor, Non small cell lung carcinoma, Vascular endothelial growth factor

INTRODUCTION

Cancer kinome is now recognized as potential target for treating cancer and comprise of more than 500 members where only few have clinical activity [1]. Tyrosine Kinase (TK) receptors are enzymes that belong to a subclass of protein kinase responsible for the control of cell growth and differentiation by transfer of a phosphate group to a tyrosine residue and thus have an important role in signal transduction. The kinase activity of the transmembrane receptor's catalytic domain is activated by the binding of growth factors (insulin, epidermal growth factor, and platelet-derived growth factor) onto its extracellular domain. However in cancer cells, overexpression of TK receptors occur due to the altered signaling cascade [2,3].

Tyrosine Kinase Inhibitors (TKI) can reversibly or irreversibly block the signaling pathway occurring in the extracellular part of the receptor by inhibiting TK phosphorylation. TK receptors can be classified into two types namely, Receptor Tyrosine Kinase (RTK) {e.g., Epidermal Growth Factor Receptor (EGFR), Platelet Derived Growth Factor Receptor (PDGFR), Fibroblast Growth Factor Receptor (FGFR)} and Non-Receptor Tyrosine Kinase (NRTK) {e.g., Cellular SRC kinase, ABL, Focal adhesion kinase and Janus Kinase (JK)}[2]. Over the years, TKI have proven efficacy as an anticancer agent for treating various malignancies. Unlike monoclonal antibodies, TKI are orally active agents with a relatively safe drug profile which are easily given in combination with other chemotherapeutic agents or radiation therapy. Another advantage is that their activity is not confined to Vascular Endothelial Growth Factor (VEGF) receptors alone, but inhibits other TK and receptors involved in tumour growth and progression. Various TKI vary in the spectrum of targeted kinases, pharmacokinetics and their adverse drug profile inspite of having a common mechanism of action. The most commonly reported ADR of TKI is skin toxicity including folliculitis occuring in more than 50% of patients [4]. Imatinib was the first TKI formulated to treat chronic myelogenous Leukaemia, followed by Erlotinib and Gefitinib that target the EGFR. Sunitinib was developed as it targeted the VEGF receptor for the treatment of renal cell carcinoma [5] and Imatinib resistant gastrointestinal stromal tumour, hence being the first TKI antagonist to be approved simultaneously for two different indications [6,7].

In this review we have given a generalized insight into the anti cancer activity, mechanism of action, and adverse drug reaction of TK whose clinical activity have been fairly understood.

Relevant studies were analysed through PUBMED and MEDLINE using MeSH search strategy by typing in the phrases "tyrosine kinase", "tyrosine kinase inhibitor", "newer tyrosine kinase inhibitors" and "investigational tyrosine kinase inhibitors". All articles from 2005 were reviewed. The drugs that were newly marketed or drugs with newer approved uses after 2015 were included in the review and anti-cancer drugs which did not fall into the TKI category were excluded from the review. Uptodate.com was the mainly used site to obtain monographs of the drugs. References from recognized studies, as well as from the previous review, were also analysed to identify any other relevant studies.

Newer Tyrosine Kinase Inhibitors:

GEFITINIB: EGFR is a target protein belonging to a family of receptors comprising of Her1 (erb-B1), Her2 (erb-B2), and Her 3(erb-B3) receptors. Mutations occuring on EGFR TK domain can lead to unwanted activation of anti-apoptic Ras signalling cascade and uncontrolled cell growth in human cells, resulting in breast and lung cancers. Gefitinib is the first selective EGFR domain inhibitor to be developed. Gefitinib inhibits the activation of anti-apoptotic Ras signal cascade by binding onto the ATP binding site of the enzyme [8,9]. Gefitinib (Iressa, Japan) was approved by the Food and Drug Administration (FDA) in May 2003 as a monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after treatment failure with platinum based and docetaxel chemotherapies as a third line agent [10]. In 2014 TRANSCOG study showed promising results in esophageal cancer patients whose tumours had additional copies of the EGFR gene. Recently, FDA approved Gefitinib on July 13, 2015, a first-line treatment for NSCLC [11]. The dosing of gefitinib is as follows:

NSCLC (metastatic with EGFR exon 19 deletions or exon 21 mutation): 250mg tablet once daily.

NSCLC (locally advanced or metastatic with EGFR mutations): 250 mg tablet once daily [10].

Gefitinib is available as tablet whose oral absorption is slow. It is metabolized extensively by the liver and caution is advised for patients with severe hepatic impairment (child pugh B and C). In case of hepatotoxicity, withhold the treatment to 14 days till AST/ALT elevations have gone to grade 1. In case of severe hepatotoxicity, discontinue the drug. Major part of the drug is excreted via feces and a small amount of drug is excreted by the urine. However, no dosage adjustments are needed in severe renal impairement, but a caution is advised in patients with CrCL<20 ml/minute. Gefitinib can be taken without regard to food. Gefitinib can cause fetal harm in pregnant women hence contraception during Gefitinib treatment is required. Presence of drug in breast milk is not known, hence its best to avoid breastfeeding during the course of therapy and 2 weeks post therapy. The most common Adverse Drug Reaction (ADR) reported are dermatologic reactions, skin rash, xeroderma, proteinuria, increased serum AST, increased serum ALT, pruritis, nausea, weakness, insomnia and fatigue [12].

Prior to initiation of Gefitinib treatment, EGFR mutation status, liver function tests, blood urea nitrogen, creatinine, electrolytes and INR/PT (with concurrent warfarin treatment) should be done. Patient should be counselled to look for signs of dermatologic, ocular, pulmonary toxicities and gastrointestinal perforations [13,14].

OSIMERTINIB (Tagrisso): Osimertinib is a third generation EGFR TKI [15] used to treat locally advanced or metastatic NSCLC and having a specific T790M mutation in gene coding EGFR. Osimertinib was identified as a breakthrough therapy in April 2014 based on its Phase I trials and provisionally approved under the FDA accelerated approval program on November 2015 [16,17]. Osimertinib binds irreversibly to EGFR proteins expressed by EGFR with a T790M mutation. Osimertinib is an irreversible EGFR inhibitor which binds to select mutant forms of EGFR and is selective for sensitising mutations and T790M resistance mutation [18].

The dosing of osimertinib is as follows (T790M EGFR mutation should be confirmed prior to treatment initiation and the patient should be unresponsive to other EGFR inhibitors) [16]:

NSCLC, metastatic with mutation are treated by administering 80mg orally, once daily until the disease progression or unacceptable toxicity occurs.

Osimertinib is available as tablet in 40 mg and 80 mg strengths. It is metabolized by the liver and no dosage adjustments have been studied in cases of moderate to severe hepatic impairment. The bioavailability of the drug is elevated by 19% with a high fat or high calorie meal. Osimertinib can be taken without any regards to meal. Even though 68% of the drug is excreted via faeces, no renal adjustment in severe renal impairement has been studied. In animal studies, the drug has the potential to cause fetal injury; hence contraception is advised till the end of treatment for both female and male patients. Excretion of the drug through breast milk is not known, hence it is best to avoid breastfeeding during the course of therapy and 2 weeks post therapy [14]. The most commonly reported ADR are skin rash, xeroderma, nail disease, pruritis, fatigue, diarrhea, lymphopenia, thrombocytopenia, anaemia, neutropenia and eye disorder.

Patients on Osimertinib should be counselled to check their ECG and electrolytes periodically specially those with a history of congenital long QTc syndrome, heart failure, electrolytes anomalies and those concomitantly taking drugs that can cause QTc prolongation. LVEF should be checked prior to the treatment and every three months while on therapy. Patients should also look out for signs of interstitial lung disease or pneumonitis, dermatologic and gastrointestinal toxicity [14,19].

CABOZANTINIB (Cabometyx, Cometriq): Cabozantinib is a VEGFR TKI shown to reduce tumour growth, metastasis and angiogenesis. In 2011, it was granted orphan drug approval by the FDA. In the third phase of a clinical trial conducted by ExelixisInc showed promising result while investigating its effect on progression free survival in medullary thyroid cancer patients [20]. Following which, a new drug application was filed and on November 29, 2012 FDA granted marketing approval for its capsule formulation (Cometriq) indicated for medullary thyroid cancer patients [21]. On April 25, 2016 Cabozantinib tablet (Cabometyx) formulation was approved by the FDA as a second line agent for treating advanced renal cancer [22]. Cabozantinib is undergoing clinical trials evaluating it's efficacy in treating prostate, ovarian, brain, melanoma, breast, non-small cell lung, hepatocellular cancers and most of them have demonstrated positive results [23]. Cabozantinib is a potent inhibitor of proinvasive receptor tyrosine kinases (RTKs), including VEGFR-1, -2, and -3 and induces apoptosis of cancer cells and suppresses tumour growth, metastasis, and angiogenesis [24]. The dosing of Cabozantinib are as follows (tablets and capsules are not interchangeable):

Advanced Renal Cell Carcinoma (RCC) 60 mg tablet is administered once daily which has to be taken till clinically benefiting or unacceptable toxicity occurs.

For metastatic medullary thyroid carcinoma 140 mg capsule is administered once daily till clinically benefiting or unacceptable toxicity occurs. However, dosing should not exceed 180 mg [25,26].

They are available in oral form, both as a tablet and capsule of 20 mg, 40 mg and 60 mg strengths.

Bioavailablity of the tablet is more when compared to capsule formulation hence the elimination half life of the tablet (99hours) is more compared to capsule (55 hours). It is metabolized by the liver. Patients with mild or moderate impairment, the initial dose should be reduced to 40 mg once daily in case of tablet and reduce the initial dose to 80 mg once daily in case of capsule. In case of severe impairment, use have not been studied hence it's better to avoid. Even though 27% of the drug is excreted by urine, no dosage adjustments are required for those whose eGFR>30 mL/minute/1.73m^2 but in less than this value, no studies have been conducted. Treatment with Cabozantinib should be withheld at least 28 days prior to surgery and resumed only after adequate wound healing has occurred [26].

The FDA has issued a US boxed warning for chances of perforations and fistulas and haemorrhage for patients taking capsule formulation. Hence patients should be counseled to look out for signs of any bleed. Cabozantinib should be taken 1 hour before or 2 hours after food. In animal studies, the drug has the potential to cause fetal injury; hence contraception is advised during and till 4 months post treatment. Excretion of the drug through breast milk is not known, hence it is best to avoid breastfeeding during the course of therapy and 4 months post therapy.

The most commonly reported ADR are hypertension, fatigue, mouth pain, palmar plantar erthyrodysesthesia (also known as hand-foot syndrome), hair discoloration, lymphocytopenia, thrombocytopenia, neutropenia, increased serum creatinine, dyspnea, increased serum triglycerides, hypocalcaemia and elevated liver enzymes are few to be noted [14].

The patient's renal functions, CBC and platelets, electrolytes, blood pressure (prior to therapy initiation and during therapy) should be stringently monitored. Patient should be counselled to look symptoms of bleed, palmar-plantar erthyrodysesthesia, proteinuria (regularly during therapy), osteonecrosis of jaw (perform oral examination prior to initiation and periodically during therapy), wound healing complications, diarrhea and stomatitis [14,27].

CRIZOTINIB (Xalkori): Crizotinib is a Anaplastic Lymphoma Kinase (ALK) and c-ros oncogene 1 inhibitor [28] used for treating selected NSCLC [29]. On August 26, 2011 FDA approved Crizotinib to treat certain locally advanced or metastatic NSCLC that have an abnormal ALK gene. In March 2016, FDA gave approval for treating ROS1-positive NSCLC [30]. Currently clinical trials are being conducted

for testing its safety and efficacy for treating anaplastic large cell lymphoma, neuroblastoma and other advanced solid tumours in adult and children population [29]. Crizotinib selectively inhibits ALK TK that decreases the proliferation of cells expressing genetic alteration. The dosing of crizotinib is as follows:

Metastatic NSCLC that are ALK or ROS1-positive patients are administered 250 mg twice daily till disease progression or unacceptable toxicities occur. It has a moderate emetic potential, hence patients have to be pre-medicated with antiemetics to prevent nausea and vomiting.

It is available as a capsule in 200 mg and 250 mg strengths. The drug can be given without any regards to meals. The bio availability is reduced by 14% if administered with high fat food. The drug is extensively metabolized by the liver and systemic exposure is increased with the severity in impairment hence caution is advised while prescribing in these patients. If hepatotoxicity occurs in patients with grade 3 or 4 with AST or ALT elevations, the drug maybe withheld and can be restarted with a reduced dose of 200 mg twice daily. If patient experiences recurrent grade 3 or 4 with AST or ALT elevations, withhold the drug and resume at a lower dose of 250 mg once daily. But, if the patient was on 250mg once daily dosing with recurrent grade 3 or 4 AST or ALT elevation, permanent discontinuation of treatment is recommended. Even though only 22% of the drug is excreted via urine, patients with creatinine clearance>30 mL/minute, not requiring dialysis, 250 mg is given once daily. Crizotinib can cause fetal harm in pregnant patients, hence contraception during treatment and at least 45 days post therapy and in male patients, contraception during and post 90 days of therapy after the final dose is recommended. Lactating mothers are advised not to breastfeed during and post 45 days of therapy [30].

The most commonly observed ADRs are visual disturbances, upper respiratory tract infections, increased ALT and AST, diarrhea, nausea; vomiting, constipation, hypophosphatemia, neuropathy, oedema and headache are few to be noted.

Patient's CBC (monthly and if grade 3 or 4 abnormalities or fever or infection), liver function test (every two weeks for the first two months, then monthly or if grade 3 or 4 abnormalities occur) and renal function test (baseline and periodic) should be done. They should also be monitored for any signs of pulmonary, cardiac and ophthalmic toxicities. Opthalmic consultations in case of vision loss is advised [14,31].

ALECTINIB (Alecensa): Alectinib is an orally active ALK TKI that is used to treat patients with advanced or recurrent ALK-positive NSCLC [31,32]. Initially it was approved on July 2014 for the treatment of ALK fusion gene positive patients with advanced or unresected NSCLC patients [33,34]. Later, on December 2015, an additional use for alectinib was approved by the US FDA to treat advanced ALK positive patients with NSCLC who could not tolerate or disease progressed on treatment with Crizotinib [35]. Recently on February 2016, J-ALEX phase III study's interim analysis on comparison between Crizotinib and Alectinib showed longer disease free progression states in patients treated with alectinib [36]. Alectinib is an inhibitor of mutated ALK genes which disrupt the normal signaling and expression leading to abnormal cell growth and increased survival rates of tumours that express these mutated proteins. However, Alectinib was found to be more potent than Crizotinib and could inhibit acquired ALK resistance mutations to Crizotinib.

The dosing of Alectinib to advanced NSCLC patients with ALK positive genes are treated with 600mg tablet twice daily till disease progression or unacceptable toxicity occurs [37]. Alectinib should be taken with food and is available as both capsules and tablet of 150 mg strengths.

The absorption of drug is increased when it's concomitantly taken with a high fat and high calorie meal. It undergoes hepatic metabolism to its active form, M4 metabolite. No dosage adjustments are required for mild impairment and no studies have been conducted to investigate its safety in moderate to severe impairment patients. In case of hepatotoxicity, if AST or ALT >3 times ULN and total bilirubin>2 times ULN, permanent discontinuation of the drug is recommended. In other cases of liver enzyme elevations, withhold the drug and restart at lower doses once the levels have become normal. The amount of drug eliminated via urine is minimal; no dosage adjustments have been studied in severe renal impairment. Data from animal study have proven to cause fetal harm, hence contraception is advised during and one week after the therapy. Contraception is also advised in male patients with female partners of reproductive potential during and three months post therapy. Excretion of the drug through breast milk is not known, hence it is best to avoid breastfeeding during the course of therapy or one week post therapy [37,38].

Common ADRs are oedema, bradycardia, fatigue, headache, skin rash, hyperglycaemia, hypokalaemia, hypophosphatemia, hyponatremia, constipation, anaemia, lymphocytopenia, increased liver function test, creatinine and creatine phosphokinase.

The patients should be counseled to monitor signs of abnormal heart rate and interstitial lung disease/pneumonitis and muscle weakness. Patients liver function test (every 2 weeks for the first month of therapy), creatinine phosphokinase and blood pressure should be monitored [14,38].

LENVATINIB (Lenvima): Lenvatinib is a multikinase inhibitor targeting against VEGFR namely, R1, R2 and R3 kinases for the treatment of differentiated thyroid cancers refractory to radioiodide treatment and advanced RCC [39,40]. In 2012, Lenvatinib was granted an orphan drug status based on positive results obtained from a trial conducted earlier in different types of thyroid cancer patients who were unresponsive to radioiodine therapy [41]. In 2015, FDA gave approval for treatment of progressive, radioiodine refractory differentiated thyroid cancer. In May 2016, Lenvatinib in combination with Everolimus combination was FDA approved for treating advanced RCC following prior one anti angiogenic therapy. Lenvatinib inhibits multiple TK receptors of VEGFR resulting in slower cancer progression and reduced rate of tumour growth. When it's combined with Everolimus in treating renal carcinoma, it exhibits enhanced antiangiogenic and antitumour activity by causing a reduction in human endothelial cell growth, tube formation and VEGF signaling when compared to either monotherapy [14].

The dosing in advanced RCC is 18mg once daily with 5mg everolimus once daily which is taken till disease progress or till unwanted toxicities occur [42] and in differentiated thyroid carcinoma 24mg once daily which is taken till disease progress or till unwanted toxicities occur [43]. Lenvatinib is available as capsule therapy pack of 8, 10, 14, 18, 20 and 24 mg daily dose. Lenvatinib can be taken without regards to meal but due to its moderate emetic action, pretreatment with antiemetics are recommended. The drug is primarily metabolized by the CYP3A enzymes; a small fraction is also metabolized non enzymatically. No dosage adjustments are required in mild or moderate hepatic impairment. Patients with severe hepatic impairment, recommended adjustments are 10mg in RCC patients and 14mg in differentiated thyroid carcinoma patients. In case of hepatic toxicity, therapy should be withheld in grade 3 or 4 hepatotoxicity and re initiated at a reduced dose when improved to grade 1. Discontinue the drug permanently if hepatic failure occurs. A 25% of the drug is excreted via urine, hence patients with CrCl<30mL/minute, dosage adjustments in RCC patients are 10mg once daily and 14mg once daily in differentiated thyroid carcinoma. In case of renal toxicity, therapy should be withheld in grade 3 or 4 renal toxicity and reinitiated at a reduced dose when improved to grade 1 [43,44].

Lenvatinib can cause fetal harm, so contraception is advised during and for atleast two weeks after completion of therapy. Breastfeeding is not recommended during therapy.

Common ADRs are hypertension, peripheral oedema, fatigue, headache, palmar plantar erythrodysesthesia, increased TSH, diarrhea, nausea, increased appetite, abdominal pain, stomatitis, proteinuria, haemorrhage, arthralgia, myalgia and cough [44].

The patient should be monitored for signs of cardiac decompensation, arterial thrombosis, reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation or fistula or haemorrhagic. Liver function, renal function, electrolyte status, TSH levels and symptoms of proteinuria should be assessed prior and after the therapy and as clinically indicated [14].

IBRUTINIB (Imbruvica): Ibrutinib is the first Bruton's Tyrosine Kinase (BTK) inhibitor that has been approved for the treatment of Chronic Lymphocytic Leukaemia (CLL), Small Lymphocytic Lymphoma (SLL), Waldenström macroglobulinemia (WM), previously treated Mantle Cell Lymphoma (MCL), and relapsed or refractory Marginal Zone Lymphoma (MZL). Ibrutinib was approved by the US FDA through the new breakthrough therapy designation pathway. In November 2013, it was initially approved to treat patients with MCL with atleast one prior therapy. Later on February 2014, Ibrutinib got its approval for treating CLL patients and on July 2014 approved for CLL patients with 17p deletion and later in March 2016 it was approved as a frontline CLL treatment Ibrutinib recieved it's approval for WM patients in January 2015. Later in May 2016, Ibrutinib got approval as a combination therapy with Bendamustine and Rituximab for patients with CLL/SLL who have undergone prior therapy. Recently it got approval for a newer indication for treating patients with MZL who have undergone prior therapy with atleast one anti-CD20 based therapy [45]. Ibrutinib is an irreversible BTK inhibitor that contributes to a reduction of malignant B cell proliferation and survival due to inhibition in activation of B-cell receptor signalling that plays a vital role in supporting the survival of malignant B-cells [14].

The dosing of Ibrutinib for different diseases is as follows:

Patients with CLL/SLL, 420 mg orally once daily is given as monotherapy or in combination with bendamustine and rituximab until disease is progressed or till intolerance to therapy.

Patients with CLL/SLL with 17p deletion or diagnosed with WM, 420 mg orally once daily is given until disease is progressed or till intolerance to therapy [45].

Patients who have undergone prior treatment for MCL are treated with 560 mg orally once daily and treated till disease progresses or till intolerance to therapy [46].

MZL patients who have relapsed are treated with 560 mg orally once daily and treated till disease progresses or till intolerance to therapy [47].

Ibrutinib is available as capsule of 240 mg dose whose absolute bioavailablity in fasting condition was 2.9% and doubled when given with meals. The drug is metabolised by the liver enzymes to its active metabolite. Patients with mild hepatic impairment are treated with reduced dose of 140 mg once daily and are avoided in patients with moderate to severe hepatic impairment. Nearly 80% of the metabolite is excreted through faeces and less than 10% of metabolite through the urine. Hence no dosage adjustments are required in mild to moderate renal impaired patients and no studies have been done to determine the dosage adjustments in severe renal impairment. Ibrutinib may cause fetal harm, hence it should not be given to pregnant patients and female of reproductive potential and males with reproductive potential female partners should avoid conception during and after one month of the last dose. Breastfeeding should be considered based on the risk to infant versus benefit to mother. Periodic assessment of blood counts, renal and hepatic functions and uric acid levels should be done. Patients check for signs of bleeding, infections, progressive multifocal encephalopathy, tumourlysis syndrome and atrial fibrillation [48].

Patient should be assessed for any cardiac risk factors or history of atrial fibrillation by performing an ECG and pregnancy status should be verified. Some of the common ADRs are peripheral oedema, fatigue, dizziness, skin rash, hyperuricaemia, diarrhoea, thrombocytopenia, neutropenia, haemorrhage, musculoskeletal pain, arthralgia, dry eye syndrome, upper respiratory tract infection and fever [14].

Summary of TKI is given below in [Table/Fig-1].

Tyrosine Kinase Inhibitors Undergoing Trials:

BRIGATINIB: Brigatinib is an investigational target anti cancer drug that is under development for treatment of ALK positive NSCLC patients resistant to Crizotinib and received breakthrough therapy designation from FDA on October 2014. It was internally discovered by ARIAD Pharmaceuticals. In May 2016, FDA gave an orphan drug approval to treat certain subtypes of NSCLC such as ALK positive, ROS1 positive or EGFR positive NSCLC. In the study, a small percentage of the population has experienced early pulmonary toxicities. Both designations were obtained on the basis of the results obtained from a continuing Phase 1/2 trial of brigatinib. This showed anti cancer activity in patients with ALK positive NSCLC inclusive of patients with active brain metastasis [14,49].

LORLATINIB: Lorlatinib is an investigational drug that has not been approved for marketing currently. It is used in the treatment of ALK positive metastatic NSCLC and also inhibits the ROS1 proto-oncogene. Usually ALK is an inactive gene that is fused with another

Anti-cancer Agent	Target	Neoplasm Type	Hepatic Adjustment	Renal Adjustment	Monitoring Parameter
Gefitinib	EGFR	NSCLC	Severe hepatoxicity: Discontinue and restart after AST/ALT is normal	Caution is advised for patients with CrCL<20mL/min	LFT, BUN, Creatinine, electrolyte, INR/PT
Osimertinib	EGFR	NSCLC with metastatic mutation	No adjustment	No adjustment	ECG, electrolyte
Cabozantinib	VEGFR	Advanced RCC, metastatic medullary thyroid carcinoma	Reduce to half dose in case of impairment	No adjustment	RFT, CBC, Platelet, electrolyte, BP
Crizotinib	ALK/ROS 1	Metastatic NSCLC	In case of elevations, with hold and restart at lower doses	250mg can be given in CrCL>30mL/min without dialysis	CBC, LFT, RFT
Alectinib	ALK	Advanced/recurrent NSCLC	AST/ALT>3X ULN and T.Bilirubin>2XULN: Discontinue	No dosage adjustments	LFT, Creatinine, Phosphokinase, BP
Levatinib	VEGFR	Thyroid carcinoma (refractory to radioiodide), RCC	Severe: 10mg for RCC and 14mg for thyroid carcinoma	CrCL<30ml/min:10mg for RCC and 14mg for thyroid carcinoma	LFT, RFT, electrolyte, TSH
Ibrutinib	BTK	CLL,SLL,WM,MCL,MZL	Mild impairment: reduce to 140mg and avoid in moderate to severe impairment	No dosage adjustment	CBC, RFT, LFT, uric acid

[Table/Fig-1]: Summary on tyrosine kinase inhibitors.

gene. When mutations occur, an ALK fusion protein is formed that causes tumour growth. ROS1 is a gene that can fuse with other genes and can increase tumour growth and its survival. It was designed to inhibit tumour mutations that causes resistance to ALK inhibitors and also penetrate the blood brain barrier which was justified from phase I trial results. Phase 2 results have shown that 100mg once daily dosing is the recommended dose of these patients. During the trials, most reported ADR's were hypercholestrolaemia and peripheral oedema [14,50].

CONCLUSION

Geftinib can be used as a first line treatment for NSCLC. Osimertinib is used for treating NSCLC with metastatic mutations. Patients who are ALK positive can be treated with Crizotinib for metastatic NSCLC and Alectinib in advanced or recurrent NSCLC which is ALK positive. But, Alectinib was proven to be more potent than Crizotinib due to its ability to inhibit acquired ALK resistance mutations to Crizotinib.

Both Cabozantinib and Lenevatinib was approved for treating RCC and Thyroid carcinomas. Cabozantinib was approved for treating metastatic medullary thyroid carcinoma and advanced RCC whereas Lenvatinib was approved for treating thyroid carcinoma refractory to iodides and RCC. Results obtained from the ongoing clinical trials of Brigatinib and Lorlatinib have demonstrated promising efficacy in treating ALK positive non small cell lung cancer in patients with brain metastasis and resistance to other TK receptors respectively. Ibrutinib was approved for the treatment of CLL, SLL, WM, previously treated MCL and relapsed or refractory MZL.

TKI have promising efficacy in treating a wide range of oncologic diseases.

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PARTICULARS OF CONTRIBUTORS:
1. Pharm D Intern, Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.
2. Pharm D Intern, Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.
3. Lecturer, Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.
4. Pharm D Intern, Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ms. KN Anila,
Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi-682041, Kerala, India.
E-mail: anilakn@aims.amrita.edu

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