International Journal of Pharmacy and Herbal Technology

e-ISSN: 2583-8962 Vol. 3, Issue 1 (January – April, 2025) pp: (3767-3777)

Tyrosine Kinase Inhibitors in Cancer Therapy: A Comprehensive Overview

Rohan More *, Sarfaraz Kazi, Sanjay K. Bais

Fabtech College of Pharmacy, Sangola, Solapur, Maharashtra, India

*Corresponding Author: rohanmore2911@gmail.com

Received Date: January 25,2025; Published Date:24, March,2025

Abstract

Tyrosine kinase inhibitors (TKIs) have transformed cancer treatment by selectively targeting crucial signalling pathways that drive tumour development and progression. This review examines the evolution, classification, and mechanisms of action of TKIs in oncology. It highlights their use across various cancers, such as chronic myeloid leukaemia, non-small cell lung cancer, and renal cell carcinoma. Key challenges, including drug resistance, side effects, and differences in patient outcomes, are discussed. Additionally, the review explores recent advancements, such as next-generation TKIs and their use in combination with immunotherapy. It aims to provide a thorough overview of the current role of TKIs in cancer care while outlining potential strategies to enhance patient outcomes in the future. This study offers a thorough analysis of TKIs, covering their pharmacological classifications, therapeutic uses, resistance mechanisms, and new developments. The emergence of first-, second-, and third-generation TKIs highlights their increasing specificity and effectiveness, especially in the treatment of cancers such gastrointestinal stromal tumors (GISTs), non-small cell lung cancer (NSCLC), and chronic myeloid leukaemia (CML). Problems like acquired resistance, side effects, and financial concerns continue to be important research topics. Combination treatments and next-generation TKIs are two recent developments that hold promise for enhancing precision medicine and improving patient outcomes.

Keywords – Tyrosine kinase inhibitors (TKIs), chronic myeloid leukaemia (CML), Non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC).

INTRODUCTION

It is known that in western countries, cancer occupies the second place in morbidity and mortality rates. Even though there are the advances in diagnosis and therapy, the rates of patient survival are low on the whole. Up until now, patients had only standard options of treatment which were either radiotherapy or chemotherapy, surgery or endocrine therapy. Tyrosine kinases belong to a group of enzymes that transfer a phosphate group from adenosine triphosphate (ATP) to tyrosine residues of proteins. Tyrosine kinase inhibitors (TKIs) are the small molecule drugs that inhibit the action of tyrosine kinase enzymes. Tyrosine kinases are a group of enzymes that modify the pathways that are used in the cells to help perform tasks such as differentiation, death, metabolism and proliferation by signalling pathways within the cell. Cancer, caused by mutations or overexpression of tyrosine kinases, can exhibit uncontrolled cell proliferation, survival, and metastasis. TKIs work by inhibiting the abnormal activity of the kinase enzyme, which subsequently interferes with oncogenic signalling pathways. The role of TKIs in targeted cancer therapy includes inhibition of tumour cell growth, encouragement for apoptosis, and specifically targeting deregulated tyrosine kinases.[1, 2]

Human protein tyrosine kinases (PTKs)

Development of specific tyrosine kinase inhibitors for cancer, with particular interest in small molecular inhibitors. Some 518 human protein kinases, or 1.7% of all human genes, have been identified by studies of the human genome.

Tyrosine kinase inhibitors are small molecules that can penetrate the cell membrane compared to the monoclonal antibodies as a carrier. [3] Monoclonal antibodies can target only secreted or cell-surface-expressed substances. Virtually all small-molecule inhibitors are hydrophobic and superb penetrators of cells that associate with intracellular signalling molecules and receptors. Therefore, small-molecule kinase inhibitors can inhibit the activation of several subsequent pathways inside cells. If necessary, tyrosine kinase inhibitors could be administered as salts and should be administered orally. For example, sunitinib is administered as sunitinib malate. [4]

The human EGFR gene on the short arm of chromosome 7, at 7p12.3-pl2.1 encodes a protein with a molecular weight of 1210 amino acids around 170 kb. The cell surface receptor EGFR plays an important role in regulating the proliferation and death of epithelial cells, as well as malignancies derived from these cells. There is a significant number of epithelial tumour cells, including head and neck region, breast, bladder, prostate, and lung cancers, that show high levels of EGFR along with the ligand. [5, 6, 7, 8] the most common mutant is EGFR VIII, an EGFR deletion. Although EGFR VIII cannot bind to ligands, it still retains tyrosine kinase activity. Activate to initiate downstream signalling pathways, independent of the binding of a site of ligand. [9] There are four transmembrane tyrosine kinase growth factor receptors, and together, they form the family of epidermal growth factor receptor (EGFR). They are; ErbB1 (EGFR/HER1), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4) (Ransom, 2004). The binding of a specific pair of ligands to the receptor. Triggers EGFR dimerization and the auto-phosphorylation of the receptor on a tyrosine residue (Arteaga, 2001). The auto-phosphorylation of the receptor triggers two major signalling pathways downstream of EGFR. The two major signalling pathways for the HER family are the PI3K-Akt pathway and the Ras-Raf MAP kinase pathway. About 15 years ago, the epidermal growth factor receptor (EGFR) was selected as a "prototype" target for drug development when research in the signal transduction field was initiated at many pharmaceutical manufacturers. The EGF family comprises four members: HER1 (c-ErbB-1/EGFR), HER2 (c-ErbB2/neu), HER3 (c-ErbB3), and HER4 (c-ErbB4), which belong to the class I receptor tyrosine kinases. All four proteins share two structural features-the cytoplasmic tyrosine kinase domain and an extracellular ligand-binding domain. They are also close homologs. The last few decades saw a plethora of evidence on the strong association of EGFR and its family members with various human cancers, including breast, lung, colorectal, ovarian, prostate, and head and neck regions.[10] Gefitinib administration into nude mice resulted in a markedly decreased formation of the tumours produced from human tumour cells and enhanced anticancer efficacy. Hormone treatment, radiation, and chemotherapy. Studies of patients with locally advanced or metastatic non-small cell lung cancer have shown that gefitinib is an antitumor agent and helps to reduce symptoms caused by the disease. [11, 12] most solid cancers of epithelial origin are known to have EGFR-TKI, including gefitinib. Tumour development can be prevented by blocking the activity of EGFR tyrosine kinase. Tumour growth, angiogenesis, metastasis, and an increase in death of tumour cells. [13, 14]

Until they build up a blood supply by stimulating the growth of new arteries arising from pre-existing host capillaries, solid tumours are restricted in their growth. Tumour cells and macrophages have been found to produce VEGF, a mitogen for vascular endothelial cells that may function in the angiogenic process. Cell surface receptors (KDR and Flt-1) having intracellular tyrosine kinase activity on the endothelium of host blood vessel form the pathway by which angiogenic signals are transmitted. Vessels linked to a tumour would be selectively targeted by inhibition of VEGF-induced thrombotic signals that would also likely reduce tumour-induced ascites. Anti-angiogenic therapy by inhibiting effects from VEGF is expected to be non-toxic and moderately tolerated in cancer patients. [15, 16, 17] VEGFR1, VEGFR2, and VEGFR3 comprise members of the VEGFR family. The family of receptors contains an extracellular sequence that is hydrophilic within the intracellular region of tyrosine kinase and seven immunoglobulin-like sequences in the extracellular domain.[18]

Angiogenesis refers to remodelling of any existing simple network of arteries and veins. It is a highly complex process that happens in several physiologic and patho-physiologic conditions. Under hypoxia, nearly all solid tumours, including the vascular endothelium surrounding them, produce vascular endothelial growth factor, or VEGF for short. It controls permeability as well as capillary growth and is very selective for the endothelium of the artery. Increased capillary density, recurrence of cancer, and decreased survival times are all correlated with increased VEGF gene expression. Therefore, rafenib has the potential to inhibit RTK activity as well as RAF-1, VGFR-2, and VGFR-3. This represents a new drug class of anti-tumour drugs with the dual targeting of VEGFR kinase and RAF kinase. Potentially, this agent might directly limit cancer cell growth by blocking the RAF/MEK/ERK cell signalling pathway. [19, 20, 21, 22] Sunitinib acts on the following among many other similar: VEGFR, PDGFR-α, PDGFR-β, CSF-1R. GISTs are gastrointestinal structural tumours, insensitive or sensitive to imatinib, and inoperable RCC responds well to the treatment. Children with these tumours or recurrent/refractory gliomas respond excellently to the treatment but some such monotherapy options need further investigation and could be contemplated in combination with chemotherapy or radiation therapy. [23, 24] A receptor tyrosine kinase, platelet-derived growth factor receptor (PDGFR), has a role in the regulation of many cellular functions including cell division, growth, and maintenance. This principally regulates blood vessel formation, wound healing, and tissue repair. PDGFR forms a family of receptor tyrosine kinases and also includes several others of PDGFR-α and PDGFR-β variants. The two types of dimers that exist include the PDGF homodimer as well as the PDGF heterodimer, both of which are bound by PDGFR. [25] PDGFRs are essential in the development of mesenchymal and vascular embryos. In tissue repair, they are involved in the proliferation and extension of smooth muscle cells and fibroblasts. Several cancers are linked to the defect in PDGFR signalling, thus it is targeted for some therapies. [26] Imatinib and other PDGFR antagonists are used in the treatment of gastrointestinal (GISTs), among other cancers. The involvement of PDGFR signalling in fibrotic disorders has led to targeting the PDGFR pathway for the treatment of a variety of diseases. [27] Though not a receptor, the protein tyrosine kinase Abl is critical to cellular growth and survival. Abnormal activation of this protein has been implicated in many cases of ALL and CML, where it operates primarily as the BCR-ABL fused protein. [28] Most cancer patients experience relief from their illness following the use of TKIs, but acquired resistance remains a challenge in targeted therapy. [29] There are multiple mechanisms of drug resistance to TKIs; fresh research is being undertaken to explore these mechanisms further and formulate treatment strategies. [30]

Classification of Tyrosine Kinase Inhibitors

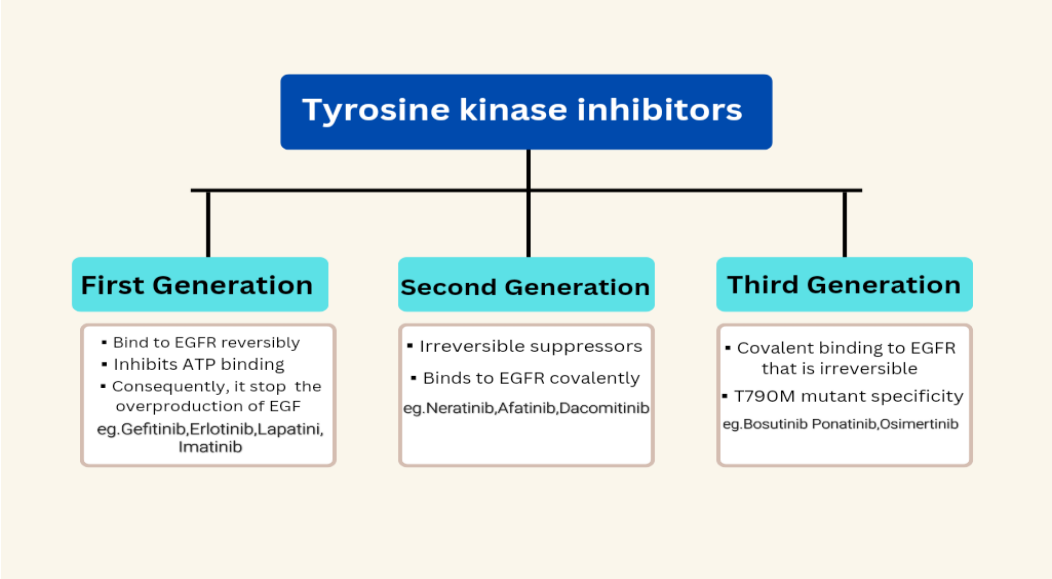

***Figure 1*:** *Tyrosine Kinase Inhibitors*

Resistance Mechanism

The T790M mutation is known to be the first acquired resistance mechanism that occurs after TKI treatment. The T790M mutation is caused by a missense mutation at the 790th codon of exon 20 of the EGFR gene, which converts threonine into methionine. In NSCLC patients who developed resistance to Gefitinib or Erlotinib, T790M mutations were found in 43 - 50% of cases. The introduction of methionine at the expense of threonine might create steric barriers that prevent hydrogen bond interactions with tyrosine kinases and TKI, making binding them ineffective. It has been found that the effect of intracellular ATP is enhanced by EGFR-sensitive, coupled with T790M mutation, whilst abrogated by TKI, causing acquired resistance. Able to cross the blood brain barrier, irreversible EGFR inhibitors have incredibly instilled hope in patients who previously failed EGFR TKI therapy. These drugs bind covalently to the ATP binding region of the kinase domain of the EGFR and at the same time act on various members of the EGFR receptor family. These drugs in theory would still enhance their efficacy, decrease chance of development of treatment resistance, and prevent T790M EGFR mutation from developing. [31, 32, 33, 34, 35, 36] The c-MET gene, which encodes a specific receptor for hepatocyte growth factor, can be located on chromosome 7 in humans. Various cancer types have been associated with dysregulation of MET, including its overexpression, mutations, and amplifications. When MET is combined with the HGF ligand, the receptor tyrosine kinase (RTK) signalling pathway is triggered, leading to increased blood vessel formation (angiogenesis), enhanced motility of epithelial tissues, and increased growth and specialization of cells. C-MET gene amplification occurs in 20% of nonsmall cell lung cancer (NSCLC) whose patients are no longer sensitive to tyrosine kinase inhibitors (TKIs), without the presence of T790M mutation. Amplification of the C-MET gene causes the ERBB3-PI3K signalling pathway to be activated even in the presence of EGFR-TKI. This subsequently leads to activation of the EGFR signalling pathway which is responsible for NSCLC TKI resistance. There have been proposals asserting that MET, thus, may be addressed after procurement of TKI agents. [37, 38, 39, 40] The transition of epithelial cells into mesenchymal cells is referred to as an epithelial mesenchymal transition. It is characterized by the loss of the epithelial phenotype including its attachment to the basement membrane, and the loss of cell polarity by epithelial cells. Instead, they assume elevated interstitial phenotypes that include motility and invasion, resistance to apoptosis, and destruction of the extracellular matrix. Studies have also revealed a relationship between tumour stem cell development, treatment resistance, territorial invasion of tumour cells and epithelial mesenchymal transitions. [41, 42]

Numerous cancers exhibit increased expression of IGF-1R, which helps to promote the transcription and translation of its proto-oncogene inducing the growth of cancerous cells. [43] The action of IGF-1R influences the PI3K and RAS/RAF/MAPK signal cascades. [44] The action of IGF-1R is pleiotropic and affects the growth metabolism and survival of cancer cells, while in cell lines there is a constant activation of the PI3K-AKT pathway, which leads to the resistance to EGFR TKIs. It has been demonstrated that preventing the activation of the IGF-1R-mediated EGFR pathway does not allow obtaining drug-resistant patients after treatment with Gefitinib. [45,46] Studies show that in particular, AKT inhibition can have a more uniform response and survival improvement in patients with high pAKT who can resist AKT-targeted therapies. This specific approach is capable of addressing the otherwise high degree of diversity in molecular resistance mechanisms that would be encountered in EGFR mutant NSCLC patients with acquired resistance to EGFR TKIs, thereby offering therapeutic benefits. [47, 48] The genetic mutation associated with lung cancer is the echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion. The genes for EML4 and ALK are found in the intracellular environment, on human chromosome number two (p21 and p23). The N-terminal EML4 inverted fusion and the ALK gene activate the PI3K/AKT/MAPK signalling pathway leading to the proliferation and differentiation of tumour cells while preventing apoptosis.

The fusion gene EML4-ALK accounts 3% to 7% of cases of NSCLC and it is most prevalent amongst young female non-smokers with adenocarcinoma. The overexpression of ALK fusion genes enhances ALK signalling, facilitating tumorigenesis and survival. Resistance to first-generation ALK inhibitors could be due to an increase in the copy number of the ALK gene (e.g. the drug crizotinib). It is more effective in combating resistant ALK mutations or amplifications than second and third generation TKIs like alectinib, brigatinib and lorlatinib respectively. Molecular testing as standard practice makes it possible to identify ALK amplification and appropriately adjust the treatment. In cases where the main signaling route (EGFR for instance) has been impeded, cancer cells can recruit redundant bypasses by utilizing different pathways or receptors, for example using MET or AXL or VEGFR pathways. Furthermore, certain classes of targeted agents (TKIs) may lead to overactivity of intracellular signaling pathways such as PI3K/AKT/mTOR or RAS/RAF/MEK/ERK, which in turn promotes cell growth. To counteract these adaptations clinical researchers are exploring the use of combination therapies, multi-kinase inhibitors, immunotherapies with activity on several pathways at the same time. [49, 50, 51]

Mechanism of Action

Tyrosine Kinase Inhibitors' (TKIs') mode of action Tyrosine kinases are the enzymes that transfer phosphate groups to tyrosine residues on proteins. Tyrosine kinase inhibitors (TKIs) block their action. Important cellular processes like growth, differentiation, survival, and signaling are regulated by this phosphorylation. Dysregulated tyrosine kinase activity causes cancer to proliferate uncontrollably, defy apoptosis, and spread. TKIs function by stopping these procedures.ATP Binding Inhibition: To phosphorylate tyrosine residues, tyrosine kinases need ATP. TKIs prevent ATP from reaching the enzyme by competitively attaching to the kinase's ATP-binding site. This effectively stops the oncogenic signaling cascade by preventing downstream signaling proteins from becoming phosphorylated. Substrate Binding Blocking: Certain TKIs prevent the kinase and its substrate from interacting. They stop downstream signaling pathways from being activated by occupying the substrate-binding site. Inhibition of Allostery: Some TKIs attach to allostery sites, which are areas outside the ATP-binding site. The conformation of the enzyme is altered by this interaction, making it inactive. Mutant Tyrosine Kinases Are Selectively Inhibited: Mutations that result in hyperactive tyrosine kinases are the cause of many malignancies. Normal kinases are largely unaffected by TKIs, which are intended to specifically block these mutant versions. Inhibition of Dual or Multiple Kinases: Certain TKIs interfere with redundant or compensatory pathways by inhibiting several tyrosine kinases at once. For instance, sorafenib affects tumor angiogenesis and growth by inhibiting the RAF, PDGFR, and VEGFR kinases. 6. Angiogenesis Inhibition: Blood vessel production in malignancies depends on VEGFR and PDGFR, which are inhibited by TKIs such as sunitinib and pazopanib. This restricts the growth and metastasis of cancers by depriving them of oxygen and nutrients. 7. Effect on Pathways of Signal Transduction: TKIs interfere with the following oncogenic signaling pathways: The PI3K/AKT/mTOR pathway controls the proliferation and survival of cells. The RAS/RAF/MEK/ERK pathway encourages the growth of cells. The JAK/STAT pathway is involved in cell survival and immune evasion. TKIs reduce systemic toxicity, promote apoptosis, inhibit tumor development, and improve therapeutic results by specifically targeting these processes. They are essential to targeted cancer treatment because of their effectiveness and specificity. [52]

Clinical Applications and Approved indications

The approaches of therapy adopted in practice and the indications for utilizing drugs in this regard include the following.

Chronic Myeloid Leukaemia (CML) & Acute Lymphoblastic Leukaemia (ALL)

Imatinib (Gleevec)

Approved for wildtype and mutated BCR-ABL CML as well as GISTs.

Dasatinib, Nilotinib, Bosutinib, Ponatinib

Indicated for CML and ALLs where the BCR-ABL mutation is present and Imatinib has failed. In the case of the T315I mutation, which is resistant to the other TKIs above, the drug Ponatinib can be utilized.

Non-Small Cell Lung Cancer (NSCLC)

Erlotinib, Gefitinib, Afatinib

Recommended in non-small cell lung cancer (NSCCL) patients who harbour EGFR activating mutations.

Osimertinib:

Indicated in NSCLC in case of EGFR mutations including T790M mutation which is involved in resistance to first and second generational TKIs.

Renal Cell Carcinoma (RCC)

Sunitinib, Pazopanib, Sorafenib:

Indicated for the treatment of advanced RCC that is anti-angiogenic through the blocking of the PDGFR and VEGFR pathways.

Cabozantinib

Advanced RCC therapy with effect on VEGFR, MET and AXL kinases.

Gastrointestinal Stromal Tumor (GIST)

Imatinib:

First-line therapy for GIST=PDGFRA or KIT mutation.

Sunitinib:

For Imatinib resistant GIST.

Hepatocellular Carcinoma (HCC)

Sorafenib:

The first line agent for advanced HCC which is an anti-angiogenic agent through VEGFR inhibition and also inhibits the RAF/MEK/ERK pathways.

Lenvatinib:

Another first line treatment for unmanageable HCC.

Breast Cancer

Lapatinib:

Used in conjunction with hormone therapy or chemotherapy (such as capecitabine) and is recommended for HER2-positive breast cancer.

Neratinib:

In supportive therapy of HER2 positive breast cancer after chemo radiotherapy.

Thyroid Cancer

Lenvatinib, Sorafenib:

Indicated for radioiodine-refractory differentiated thyroid carcinoma (DTC).

Cabozantinib, Vandetanib:

Kinase targeting, including VEGFR and RET, is used in the treatment of medullary thyroid carcinoma.

Cholangiocarcinoma (Bile Duct Cancer)

Pemigatinib:

Is approved for use in patients with cholangiocarcinoma with FGFR2 fusion positivity.

Bladder Cancer

Erdafitinib**:**

For metastatic bladder cancer with dysregulation of FGFR3 or FGFR2.

Mantle Cell Lymphoma (MCL)

Acalabrutinib, Ibrutinib, Zanubrutinib:
Aimed at preventing B-cell signalling in MCL and other lymphomas by targeting Bruton's Tyrosine kinase (BTK). [53]

Recent Advances and Future Directions in Tyrosine Kinase Inhibitors for Cancer Therapy

TKI research has recently advanced to include the creation of next-generation inhibitors that are intended to overcome drug resistance to earlier versions. These consist of compounds that target mutations like BCR-ABL mutations in chronic myeloid leukaemia (CML) or T790M In non-small cell lung cancer (NSCLC). The efficacy of treatment and patient survival may be improved by combination treatments, which combine TKIs with immunotherapies (such as checkpoint inhibitors). Future options to consider include investigating new targets within tyrosine kinase pathways, designing TKIs with increased specificity to minimise off-target effects, and utilising artificial intelligence to optimise individualised treatment plans. Enhancing patient selection, reducing resistance, and creating customised treatment plans will all be made possible by developments in biomarker identification. These initiatives seek to optimise treatment results and establish TKI-based treatments as a sustainable oncology treatment option. [54, 55, 56]

Advantages

Targeted Treatment: Compared to conventional chemotherapy, TKIs have less systemic toxicity because they specifically target particular tyrosine kinases involved in the development of cancer cells while sparing healthy cells.
Easy Management: Since the majority of TKIs are oral drugs, patients find them more convenient than intravenous chemotherapy.
Widespread Use throughout Cancers: It works well for treating a number of tumors, such as renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and chronic myeloid leukemia (CML).
Diminished Adverse Reactions: TKI side effects, such as tiredness, diarrhea, and rash, are frequently easier to control and are typically less severe than those of chemotherapy.
Powerful against Particular Mutations: TKIs improve patient outcomes by being very effective against certain genetic alterations, such as EGFR in NSCLC or BCR-ABL in CML.
Potential for Combinations: To increase effectiveness, TKIs can be used in conjunction with other treatments (such as immunotherapy or chemotherapy).
Overcoming Resistance to Chemotherapy: For malignancies that don't respond to conventional chemotherapy, TKIs provide an option.
Enhanced Survival of Patients: For patients with specific malignancies, such CML and NSCLC, TKIs have greatly improved survival rates and quality of life. [57]

Limitations

Development of Resistance: Secondary mutations (such as T790M in EGFR-mutated NSCLC) or the activation of alternative pathways might cause cancer cells to become resistant. Example: T315I mutation-induced imatinib resistance in CML.
Restricted Purview: Because TKIs only work on malignancies caused by particular tyrosine kinase mutations, they are not as useful for cancers that are genetically complex or unidentified. 3. Negative

Impacts

TKIs still have side effects, however they are not as bad as chemotherapy. These include: Heart failure and hypertension are cardiovascular problems that can be treated with VEGFR inhibitors like sunitinib. Dry skin and rashes are signs of skin toxicity. Hepatotoxicity, nausea, and diarrhea are digestive problems.

Expensive

Because TKIs are frequently costly, many patients cannot afford them, particularly in settings with limited resources.

Long-Term Usage Difficulties

Long-term use can result in financial strain, compliance problems, and cumulative negative effects.

Heterogeneity of Tumors

The effectiveness of TKIs may be diminished by tumors that have several driver mutations or that change while being treated.

Limited Effectiveness in Later Stages

TKIs may be less helpful in cases of advanced metastases or malignancies that have been extensively pretreated. They are more successful in early-stage cancers.

Interactions with Drugs

Treatment plans become more difficult when TKIs combine with other drugs and foods (e.g., CYP450 enzyme interactions).

Effectiveness That Is Not Universal

Because of genetic or epigenetic variations, not every patient with the target mutation responds to treatment [58].

CONCLUSION

Tyrosine kinase inhibitors (TKIs) have become potent weapons in the fight against cancer because they provide a focused strategy that has enhanced patient outcomes in a large number of cases. However, problems including side effects, response variability, and medication resistance need to be continuously addressed. More selective TKIs, creative therapy combos, and the application of biomarkers to customise care for specific patients will be necessary for future advancements. With continued advancements in research, TKIs are anticipated to play a crucial role in customised cancer care, contributing to increased efficacy, less toxicity, and better long-term outcomes for patients.

REFERENCES

1. G. Manning, D. B. Whyte, R. Martinez, T. Hunter, S. Sudarsanam, the Protein Kinase Complements of the Human Genome, Journal of Science,2002:298(7):34-39.
2. Krupa, N. Srinivasan, the Repertoire of Protein Kinases Encoded in the Draft Version of the Human Genome a Typical Variations and Uncommon Domain Combinations, Journal of Molecular Biology,2002:3(4):7-10.
3. Imai K. Takaoka, A Comparing Antibody and Small Molecule Therapies for Cancer, Journal of Molecular Cancer Therapeutics,2006:6(10):714–727.
4. V. L. Goodman, E. P. Rock, R. Dagher , R. P. Ramchandani , S. Abraham , J. V. Gobburu , B. P. Booth, S. L.Verbois, D. E. Morse, C. Y. Liang, N. Chidambaram, J. X. Jiang,S. Tang, K. Mahjoob , R. Justice, R. Pazdur, Approval Summary Sunitinib for the Treatment of Imatinib Refractory or Intolerant Gastrointestinal Stromal Tumors and Advanced Renal Cell Carcinoma, Journal of Clinical Cancer Research,2007:13(9):1367–1373.
5. B. J. Druker, Activity of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in the Treatment of Chronic Myeloid Leukemia, Journal of New England Medicine,2001:344(14):1031-1037.
6. C. Wertheimer, J. Siedlecki, D. Kook, W. J. Mayer, A. Wolf, A. Klingenstein, A. Kampik, EGFR Inhibitor Gefitinib Attenuates Posterior Capsule Opacification in Vitro and in the Ex Vivo Human Capsular Bag Model, Journal of Graefe's Archive for Clinical and Experimental Ophthalmology, 2015:253(6):409–417.
7. C. W. S. Tong, Drug Combination Approach to Overcome Resistance to EGFR Tyrosine Kinase Inhibitors in Lung Cancer, Journal of Cancer Letters,2017:405(4):100–110.

8. B. R. Voldborg, L. Damstrup, M. Spang Thomsen, H. S. Poulsen, Epidermal Growth Factor Receptor and Egf-R Mutations Function and Possible Role in Clinical Trials, Journal of Annals of Oncology,1997:12(2):1197-1206.
9. H. A. Blair, G. L. Plosker, Sorafenib a Review of its use in Patients with Radioactive Iodine-Refractory Metastatic Differentiated Thyroid Carcinoma, Journal of Targeted Oncology, 2015:10(6):171–185.
10. N. Nishida, M. Kitano, T. Sakurai, M. Kudo, Molecular Mechanism and Prediction of Sorafenib Chemo Resistance in Human Hepatocellular Carcinoma, Journal of Digestive Diseases, 2015:33(12):771–779.
11. C. Nagel, S. Armeanu-Ebinger, Dewerth, S. W, Warmann, J. Fuchs, Anti-tumor Activity of Sorafenib in a Model of a Paediatric Hepatocellular Carcinoma, Journal of National Library of Medicine, 2015:331(1):97–104.
12. J. Mei, X. Zhu, VEGFR, RET, and RAF/MEK/ERK Pathway Take Part in the Inhibition of Osteosarcoma MG63 Cells with Sorafenib Treatment, Journal of Cell Biochemistry Biophysics, 2014:69(33):151–156.
13. S. Kalra, B. I. Rini, E. Jonasch, Alternate Sunitinib Schedules in Patients with Metastatic Renal Cell Carcinoma, Journal of Annals Oncology,2015:26(7):1300–1304.
14. Imbulgoda, D. Y. Heng, C. Kollmannsberger, Sunitinib in the Treatment of Advanced Solid Tumors, Journal of Current Opinion in Oncology,2014:201(24):165–184.
15. M. Shibuya, VEGFR and Type-V RTK Activation and Signaling, Journal of Cold Spring Harb Perspectives Biology,2013:5(4):35-37.
16. N. Ferrara, Vascular Endothelial Growth Factor, Journal of Trends in Cardiovascular Medicine, 1993:3(6):244-250.
17. W. Koelch, G. Martiny-Baron, A. Kieser, A. D. Marme, Regulation of the Expression of VEGF/VPS and its Receptors Role in Tumor Angiogenesis, Journal of Breast Cancer Research and Treatment,1995:36(12):139-155.
18. G. Breier, W. Risau, The Role of Vascular Endothelial Growth Factor in Blood Vessel Formation, Journal of Trends in Biochemical Sciences,1996:6(9):454-456.
19. C. H. Yang, H. C. Chou, C. L.Yeh, H. W. Cheng, I. C. Chang, K. J. Liu , G. C.Chang ,T. F. Tsai, EGFR Over-Expression in Non-Small Cell Lung Cancers Harboring EGFR Mutations is Associated with Marked Down-Regulation of CD82, Journal of Biochemistry Biophysics Acta Molecular Basis of Disease,2015:1852(7):1540–1549.
20. H. J. Lee, A. N. Seo, E. J. Kim, M. H. Jang,Y. J. Kim, S. W. Kim, H. S. Ryu, I. A. Park, Prognostic and Predictive Values of EGFR Overexpression and EGFR Copy Number Alteration in HER2-Positive Breast Cancer, Journal of Clinical Oncology,2015:112(21):103–111.
21. Y. H. Han, M. R. Abdul Hamid, P. U. Telisinghe, J. B. Haji Hussin, M. Mabruk, Overexpression of EGFR Protein in Bruneian Lung Cancer Patients**,** Journal of Asian Pacific Cancer Prevention,2015:16(9):233–237.
22. S. H. Park, High EGFR Gene Copy Number Predicts Poor Outcome in Triple-Negative Breast Cancer, Journal of Modern Pathology,2014:27(2):1212–1222.
23. F. Rahman, M. H. Korashy, M. G. Kassem, Pharmacological Profile and Applications of Gefitinib, Journal of Profiles of Drug Substances Excipients and Related Methodology, 2014:39(1):239–264.
24. S. Dhillon, Gefitinib A Review of its Use in Adults with Advanced Non-Small Cell Lung Cancer, Journal of Targeted Oncology,2015:10(3):153–170.
25. C. H. Heldin, B. Westermark, Mechanism of Action and In Vivo Role of Platelet-derived Growth Factor, Journal of Physiological Reviews,1999:79(4):1289-1316.

26. S.M. Wilhelm, Discovery and Development of Imatinib as a Therapeutic Agent for Gastrointestinal Stromal Tumor, Journal of Nature Reviews Drug Discovery,2006:5(4):297-303.
27. P. Zymotic, the Role of PDGFR Signaling in Cardiac Remodelling, Journal of Circulation, 2006:135(10):999-1009.
28. J. C. Chen, C. F. Chiu, Y. W. Chang, C. F. Tseng, H. A. Chen, Suppression of Dicer Increases Sensitivity to Gefitinib in Human Lung Cancer Cells, Journal of Annals of Surgical Oncology, 2014:21(4):555–563.
29. D. R. Camidge, W. Pao, L. V. Sequist, Acquired Resistance to TKIs in Solid Tumours Learning from Lung Cancer, Journal of Nature Review on Clinical Oncology,2014:11(8):473–481.
30. M. Watanabe, T. Kawaguchi, Ultra-Sensitive Detection of the Pretreatment EGFR T790M Mutation in Non-Small Cell Lung Cancer Patients with an EGFR Activating Mutation Using Droplet Digital PCR, Journal of Oncotarget,2015:21(6):3552–3560.
31. J. L. Kuiper, D. A. Heideman, E. Thunnissen, M. A. Paul, Incidence of T790M Mutation in (Sequential) Rebiopsies in EGFR Mutated NSCLC-Patients, Journal of Lung Cancer, 2014:85(5):19–24.
32. Hata, N. Katakami, Rebiopsy of Non-Small Cell Lung Cancer Patients with Acquired Resistance to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Comparison Between T790M Mutation-Positive and Mutation-Negative Populations, Journal of Thorasis Oncology, 2013:119(1):4325–4332.
33. M. G. Denis, A. Vallee, EGFR T790M Resistance Mutation in Non-Small-Cell Lung Carcinoma, Journal of Clinical Chemistry and Laboratory Medicine,2015:444(5):81–85.
34. C. H. Yun, K. E. Mengwasser, The T790M Mutation in EGFR Kinase Causes Drug Resistance by Increasing the Affinity for ATP, Journal of Proceedings of the National Academy of Sciences of the United States of America,2008:105(9):2070–2075.
35. P. Bordi, M. Tiseo, B. Bortesi, Overcoming T790M Driven Acquired Resistance to EGFR-TKIs in NSCLC with Afatinib, Journal of a Case Report Tumori,2014:100(4):20–23.
36. S. Wang, S. Cang, D. Liu, Third-Generation Inhibitors Targeting EGFR T790M Mutation in Advanced Non-Small Cell Lung Cancer, Journal of Hametology and Oncology,2016:9(2):34-40.
37. Y. Kwak, S. I. Kim, C-MET Overexpression and Amplification in Gliomas, International Journal of Clinical and Experimental Pathology,2015:8(22):14932–14938.
38. D. Chen, C. Xu, Comparison of Consistency of Detecting c-MET Gene Amplification in Peripheral Blood and Tumor Tissue of Non-Small Cell Lung Cancer Patients, Journal of Thoracic Disease,2015:11(1):63–67.
39. D. Presutti, S. Santini, MET Gene Amplification and MET Receptor Activation are not sufficient to Predict Efficacy of Combined MET and EGFR Inhibitors in EGFR TKI Resistant NSCLC Cells, Journal of Frontiers Oncology,2015:10(12):35-39
40. H. Kawakami, I. Okamoto, Amplification as a Potential Therapeutic Target in Gastric Cancer, Journal of OncologyTarget,2013:4(21):9–17
41. L. Zhang, J. Zhou, H. Chen, Cigarette Smoke Extract Exposure Induces EGFR-TKI Resistance in EGFR-Mutated NSCLC Via Mediating Src Activation, Journal of Lung Cancer,2016:93(8):35–42.
42. L. Huang, Mechanisms of Resistance to EGFR Tyrosine Kinase Inhibitors, Journal of Acta Pharmacological Sinica B,2015:5(4):390–401.

43. W. Cai, M. Sakaguchi, A. Kleinridders, Domain Dependent Effects of Insulin and IGF-1 Receptors on Signalling and Gene Expression, Journal of Nature Communication, 2017:8(2):14892-14897.
44. K. Mills, S. Gusscott, C. E. Jenkins, S. H. Lam, V. Giambra, M. Pollak, A. P. Weng, IGF1R Derived PI3K/AKT Signaling Maintains Growth in a Subset of Human T Cell Acute Lymphoblastic Leukemias, Journal of Journal of Frontiers Oncology,2016:11(5):566-577.
45. N. Tang, R. C. Thompson, B. C. Mobley, InsR/IGF1R Pathway Mediates Resistance to EGFR Inhibitors in Glioblastoma, Journal of Clinical Cancer Research,2016:22(6):1767–1776.
46. E. Park, S. Y. Park, H. Kim, P. L. Sun, Membranous Insulin-like Growth Factor-1 Receptor (IGF1R) Expression is Predictive of Poor Prognosis in Patients with Epidermal Growth Factor Receptor (EGFR)-Mutant Lung Adenocarcinoma, Journal Pathology and Translational Medicine, 2015:49(5):382–388.
47. K. Jacobsen, J. Bertran-Alamillo, M. A. Molina, Convergent Akt Activation Drives Acquired EGFR Inhibitor Resistance in Lung Cancer, Journal of Nature Communication,2017:8(2);410-418.
48. L. Fang, L. Dong, X. Zhang, Y. Chai, Resistance to Epithelial Growth Factor Receptor Tyrosine Kinase Inhibitors in a Patient with Transformation from Lung Adenocarcinoma to Small Cell Lung Cancer, Journal of Oncology Letters,2017:14(3):593-598.
49. M. Soda, Y. L. Choi, M. Enomoto, S. Takada, Y. Yamashita, Identification of the Transforming EML4-ALK Fusion Gene in Non-Small-Cell Lung Cancer, Journal of Nature,2007:448(6):561–566.
50. H. Mano, the EML4-ALK Oncogene Targeting an Essential Growth Driver in Human Cancer, Journal of Cancer Science,2015:91(3):193–201.
51. W. B. M. Han, Clinical Meaning of EML4-ALK Fusion Gene in Non-Small Cell Lung Cancer, Journal of Molecular and Clinical Oncology, 2013:16(4):97–101.
52. Zhang J. Yang, P. L. Gray, Targeting Cancer with Small Molecule Kinase Inhibitors, Journal of Nature Reviews Cancer, 2009:9(1):28-39.
53. Hochhaus, Treatment-Free Remission in Patients with Chronic Myeloid Leukemia in Chronic Phase after Stopping Imatinib, Journal of Clinical Oncology,2017:35(26):2981-2990.
54. Shirish B. Nagansurkar, Sanjay K. Bais, Amol V. Pore, Sarfaraz M. Kazi, Nikita D. Pawar, Formulation and Quality Control of Herbal Mouthwash Containing Natural Extracts of Tulsi, Neem, Turmeric, Clove, Liquorice and Peppermint, International Journal of Pharmacy and Herbal Technology,2023:1(2):63-72.
55. Yogesh B. Raut, Sanjay K. Bais, Sakshi Wale, Rohan More, Pratiksha Tavate, Unlocking Nature's Pharmacy the Power of Herbal Medicine in Modern Healthcare, International Journal of Pharmacy and Herbal Technology,2024:2(2):1598-1602.
56. S. R. Mane, Sanjay K. Bais, Aditya Mali, Review on Green Chemistry and Catalysis, International Journal of Pharmacy and Herbal Technology, 2024:2(1):418-427.
57. Hochhaus, Treatment-Free Remission in Patients with Chronic Myeloid Leukemia in Chronic Phase after Stopping Imatinib, Journal of Clinical Oncology,2017:35(26):2981–2990.
58. S. V. Rajkumar, The High Cost of Cancer Drugs and What We Can do about it, Journal of Mayo Clinic Proceeding,2020:95(7):1291–1293.