Review Article

Leukaemia Management by Inhibiting Tyrosine Kinases (Review)

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Abstract:

Leukemia is a group of hematological malignancies that usually begin at the bone marrow resulting in an increased number of abnormal blood cells. These abnormal cells do not fully develop and differentiate leading to the formation of new cells called blast cells. The formation of these malformed cells comes from either the aberrant signaling or mutation of tyrosine kinases. Tyrosine kinases play a crucial role in many biological processes such as cell proliferation and growth, migration, differentiation, survival, and metabolism. Abnormalities in these enzymes lead to cancer formation and the necessity to treat affected patients. Tyrosine kinase inhibitors have been shown to play an increasing and significant role in treating cancers and inhibiting aberrant signals. However these drugs have been shown to have some limits such as side effects which can be quite severe at times, but also they have been met with resistance by cancer cells. This article aims to show how these kinases work, which pathways or proteins they inhibit, and some of the most successful drugs which are being used and tested to treat leukemia patients.

Keywords: *Leukemia, tyrosine kinase, inhibitor, cancer.*

Introduction

Leukemia is a group of haematological malignant disorders consisting of aberrant signaling and an increased number of white blood cells in the blood or bone marrow. According to the International Agency for Research on Cancer (World Health Organization 2020), the number of new cases for leukemia was nearing 475 thousand and the number of people dying from it was 312 thousand. Leukemia is the most common cancer in children and young adults, making up for one out of three cancers affecting these ages. Children are mostly affected by acute lymphocytic leukemia (ALL), whereas the remaining fall victim to acute myeloid leukemia (AML) (American Cancer Society 2020). There are four major types of leukemia which have only one thing in common; they all begin in the bone marrow:

1) Acute lymphocytic leukaemia (ALL)
2) Acute myeloid leukaemia (AML)
3) Chronic lymphocytic leukaemia (CLL)
4) Chronic myeloid leukaemia (CML)

Acute myeloid leukemia is the most common type of leukemia in adults, reported at 30%, which also has the lowest prognosis **(**Mizuki et al., 2003, Yamamoto et al., 2008**)**. ALL is predominantly found in children, peaking between the ages of 2 and 5 **(**Inaba H. et al, 2013**)**. CML accounts for 15% of leukemias in adults ranging between the ages of 45 to 55 years old **(**Faderl S. et al., 1999**)**. CLL is an incurable lymphoproliferative disorder that leads to an increased number of monoclonal mature B cells in the blood and bone marrow **(**Francesc Bosch and Riccardo Dalla Favera, 2019**)**.

Tyrosine kinases (TKs) are a group of enzymes, part of a superfamily responsible for binding phosphate groups with amino acids, such as serine or threonine. They also mediate the transfer of phosphate from ATP to other amino acids to produce a signal able to initiate different cellular processes. They take part in critical steps of cell communication, differentiation, cell metabolism, survival, migration and controls the cell cycle **(**Ullrich and Schlessinger 1990**)**.

TKs can be classified into two major categories: receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (NRTKs). 58 different known receptor tyrosine kinases have a similar molecular structure **(**Manning et al., 2002**)**, comprised of an extracellular ligand-binding region, an intracellular region, a single transmembrane helix, a tyrosine kinase domain, and the terminal carboxyl- tail (C-). RTKs are important transmembrane receptors that include major receptors such as platelet-derived growth factor receptors (PDGFR), vascular endothelial growth factor receptors (VEGFR), insulin receptors (InsR) and the epidermal growth factor receptors (EGFR), and human growth factor receptor-2 (HER2) part of the ErbB receptor family **(**Thomson R., et al. 2020**)**.

Mechanism of action

Tyrosine kinases are enzymes that selectively catalyze and a phosphorylases tyrosine residue in different substrates and transfer phosphoryl groups from an ATP donor to a recipient molecule. This phosphorylation changes the function of the different types of substrates where they are found **(**Cox M., et al. 2008**)**. Different ligands employ different approaches to stabilize their structural conformation. Tyrosine kinases are involved in a wide variety of cellular signaling and responses by acting as mediators and helping with critical processes as cell proliferation, differentiation, migration, metabolism, and apoptosis **(**Manash K. Paul and Anup K. Mukhopadhyay., 2004**)**. Figure 1 shows a schematic representation of the mechanism of action of tyrosine kinases:

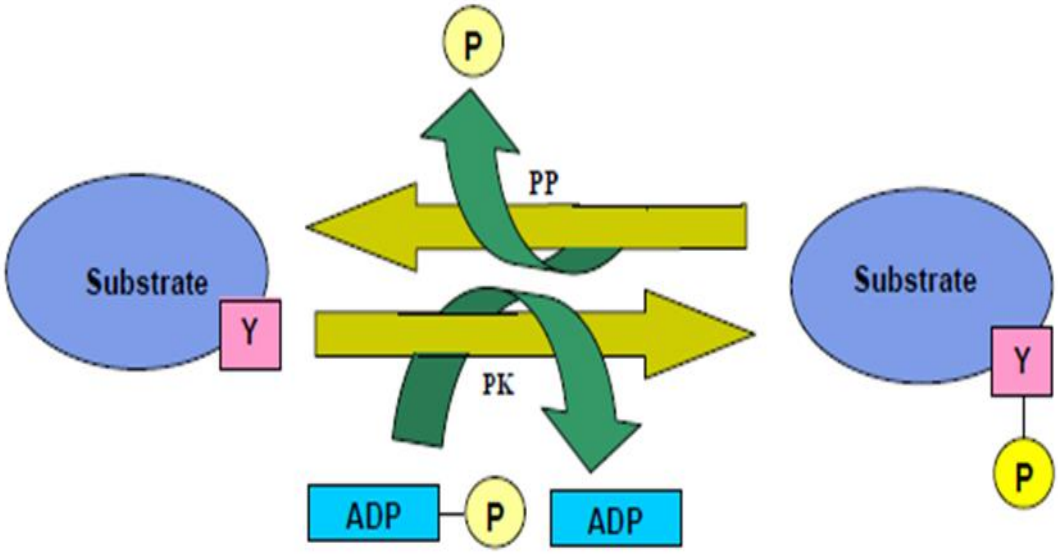

Figure 1: Schematic representation of the mechanism of action of tyrosine.

***Manash K. Paul and Anup K. Mukhopadhyay., 2004**

Normally the level of RTK activity is in balance thanks to the mechanism of antagonism between tyrosine kinases and tyrosine phosphatases **(**Ostman A, Bohmer FD 2001**)**. When this balance is no longer controlled or when we have overexpression of these kinases we see an increase in the intrinsic activity of the TKs which leads to a disruption of the cell growth/proliferation and apoptosis mechanism **(**Schlessinger J., 2000**)**. This overexpression has been linked to various cancers in the human body because of the aberrant signaling which in turn dysregulates signal cascades and results in tumors or other kinds of severe diseases **(**Bhullar K., et al., 2018**)**. Abnormal RTKs activation can grant them oncogenic abilities. 4 different major ways can lead to cancer by RTKs:

a) Activation by gain of function mutations

b) Overexpression and genomic amplification

c) Chromosomal rearrangement

d) Autocrine activation

Tyrosine Kinase Inhibitors

Since RTKs play a very major and important role in cancer development and progression they have become more appealing as therapeutic targets for treating patients with cancer, especially leukemia. One way which has shown a lot of promise is the usage of tyrosine kinase inhibitors (TKIs) which can stop the aberrant signaling from mutated TKs. These inhibitors can bind in either a reversible or irreversible way. According to **(**Wu P, et al in 2015**)** there are five major types of inhibitors classified based on the conformation of binding and DFG motif:

1) Type I inhibitors: they bind competitively to the ATP site of active tyrosine kinases. The aspartate residue of the DFG motif is placed facing forward of the active catalytic site of the TKs.

2) Type II inhibitors: bind the inactive form of TKs and the aspartate residue projects outward from the ATP binding site.

3) Type III inhibitors: the inhibitors bind only to an allosteric site near the ATP, but never interacting with it.

4) Type IV inhibitors: their allosteric binding region is very far from the ATP binding site.

5) Type V inhibitors: this kind of inhibitor show more than one binding approach.

Imatinib mesylate (Gleevec) is a first-generation inhibitor for mutated TKs. It is a salt of imatinib that has antineoplastic activity. This compound binds to tyrosine kinases leading to an inhibition of ATP binding thus preventing phosphorylation which in turn doesn't turn on the signal for growth receptors and their downstream signaling pathways. Imatinib inhibits TKs which are activated by the bar-all oncogene and c-kit. This inhibition results in lower proliferation and increased apoptosis of cancer cells such as CML or ALL **(**PubChem 2021**)**.

Sorafenib is a drug that targets growth signaling and angiogenesis. This compound blocks RAF kinase, part of the MEK/Erk signaling pathway. This pathway is responsible for controlling cell division and proliferation and thus by inhibiting RAF this pathway is halted and cancer cells have lower proliferation. Apart from the RAF enzyme, sorafenib also inhibits the VEGFR-2 signaling pathway which leads to a blocking of tumor angiogenesis. A study by **(**Rahmani et al., 2007**)** clearly shows that sorafenib in relevant concentrations (10 – 15uM) quite strongly induces apoptosis in cells that are resistant to imatinib mesylate.

Sunitinib derivates from indolinone and inhibits aberrant tyrosine kinase activity. It blocks the VEGFR-2 and PDGFRb signaling pathways leading to angiogenesis and cell proliferation inhibition. Different studies have shown an anticancer ability of Fms-like tyrosine kinase 3 by inhibiting its phosphorylation and inducing transient blast count reduction (Fiedler et al, 2015; Fischer et al, 2010). Dasatinib is an inhibitor of the SRC protein, part of the tyrosine kinase family. It reduces the activity of growth promotion characterizing TKs. It has a lower affinity for the bar-abl kinase thus it can overcome the resistance CML cells have for imatinib **(**Druker et al, 2001**)**.

Quizartinib (AC220) is a class III drug compound that selectively inhibits the FLT3 tyrosine kinase which leads to reduction of proliferation activity and increase of apoptosis **(**Zhou F., et al, 2019**)**. The usage of these compounds has been shown to have promising and specific results. Inhibition of aberrant tyrosine kinase signal and blocking of growth factor receptors have made it possible for leukemia patients to have a wider array of options for treatment. Even though options are being made available there is still the issue of adverse effects these compounds exhibit in leukemia patients. Patients exhibiting side effects were more than 80% of those tested induced by toxicity from drug administration **(**Fu Y., 2018**)**. Some of the most common side effects are hypertension, diarrhea, nausea, anemia, vomiting, fever, fatigue, weight loss, QT prolongation. Some of the more adverse reactions as a result of drug toxicity were skin color change, hand-foot skin reactions, leukopenia, proteinuria, liver hypertoxicity, and oedemas.

Discussion

Tyrosine kinases play an important role in a wide array of mechanisms critical for normal physiological processes. Their role in cell proliferation, migration, survival, differentiation, and apoptosis tells of the role they have in the human body and that research in better understanding and studying these kinases is vital. Aberrant signaling of different abnormalities that target tyrosine kinases can lead to severe hematological diseases. Leukemia is a disease that targets the white blood cells or bone marrow leading to the abnormal count of leukocytes and severe damage to the affected individual.

Since treatment is very limited and there is no cure, the appearance of tyrosine kinase inhibitors has opened new approaches to combat this disease. They have revolutionized the management of patients with leukemia and improved both their overall survival and lifestyle. Most of them have been quite promising for some time and are usually safe to be used but there remains the fact of the side effects, sometimes severe, that patients are experiencing from these drugs. The search for a new generation of drugs is underway which hopefully could lead to better results, meanwhile reducing the side effects, toxicity, or even the resistance that leukemia cancer cells show when treated with TKIs. Newer potent, enhanced, and safer TKI drugs are a promising prospect for affected people which could lead to advanced treatment methods.

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