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Effects of Tyrosine Kinase Inhibitors on Chronic Myeloid Leukemia Patients: A Narrative Review

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Abstract: ***Tyrosine kinase inhibitors (TKI) are a type of targeted therapy which have already shown growing evidence in the treatment of chronic myeloid leukaemia patients. This is a comprehensive review of the effects of tyrosine kinase inhibitors on chronic myeloid leukaemia patients. The natural course of CML has been greatly modified by TKIs, which have dramatically transformed patient survival. Second-generation tyrosine kinase inhibitors used in first-line therapy led to more rapid and profound molecular remission with different adverse event profiles as compared to imatinib (1st generation). There has been a lot of research on the medical effects of tyrosine kinase inhibitors and their mechanism of action. However, even though they are extremely effective, there have been incidences of resistance to tyrosine kinase inhibitors. There have been higher cases of patients not responding to TKIs (Primary resistance) or relapse after treatment (Secondary resistance). One of the most common tyrosine kinase inhibitors is Imatinib. It blocks the BCR-ABL fusion protein. There are three second-generation agents (nilotinib, dasatinib, bosutinib) that are more effective than Imatinib, but they have not shown long-lasting effects. Asciminib is used if the initial 1st line therapy fails. BCR-ABL mutational analysis is important and has to be done for the treatment of CML if the initial therapy fails. Single point mutations of BCR-ABL are the most common cause of Imatinib resistance. Conventional Sanger sequencing is done to check for these mutations, but Next-generation sequencing is the newest modality to test for them.***

Keywords: CML; Tyrosine kinase inhibtors; Chronic Myeloid Leukemia; Elderly; Chronic Granulocytic Leukemia

1. Introduction

Chronic myeloid leukaemia (CML) / BCR-ABL1-positive23 is a chronic disease that requires long-term therapy and responds well to treatment with tyrosine kinase inhibitors (TKI) (1). TKIs have revolutionized the treatment of CML and significantly improved patient survival (2).

Second-generation agents used in first-line therapy provide faster and more profound molecular improvements with different side effects than imatinib (3). TKIs that target BCR-ABL1 are highly effective. However, some patients may not respond (primary resistance) or relapse after an initial response (secondary resistance). There are many educational gaps in understanding how tyrosine kinase inhibitors function in chronic myeloid leukaemia. In a limited percentage of patients, the transition from the chronic to the blastic phase (BP), which is marked by a poor prognosis, occurs concurrently with or soon after the development of resistance (4). One key mechanism of TKI resistance in CML is point mutations in the ABL1 kinase domain (KD) (5). The most common adverse effects related to the cardiovascular system include heart failure, hypertension, atrial fibrillation, diminished cardiac function, and sudden death. There are significant knowledge gaps in the creation of effective medication and treatment guidelines since the possible mechanisms underlying these side effects are unclear (6). At the moment, pediatric patients can choose among three FDA-approved TKIs: imatinib, dasatinib, and nilotinib (7). Regardless of the TKI selected as frontline, it is important to identify noncompliance or treatment failure as soon as feasible because doing so increases the likelihood of getting the best potential response (8).

This literature review aims to demonstrate the efficacy of TKIs in CML patients, to examine the evolution of treatment strategies, the clinical outcomes associated with different TKIs, and the challenges that remain. in the long-term management of this disease.

2. Discussion

A tyrosine kinase inhibitor is a drug that interferes with the communication, growth and division of cells by blocking the tyrosine kinase in our body (9). Since the early 2000s, TKIs have been utilized to treat various cancers such as chronic myelogenous leukaemia (10). These are a class of drugs that actively inhibit protein kinase signal transduction pathways.

Chronic myeloid leukaemia (CML) is characterized by abnormal culture and proliferation of white blood cells in only one main compartment, the ‘bone marrow’. However, the rate of the disease tells us when it is found in other areas than the bone marrow (11,12). It is also known as chronic granulocytic leukaemia. Table 1 below describes the stages of progression of Chronic Myeloid Leukemia:

Table 1

	Median duration of treatment	Blasts	Symptoms
Stage of CML			
1)Chronic Phase	5-6 years	10-15%	Asymptomatic
2)Accelerated phase	6-9 months	>15%, but <30%	a) Weight loss b) Tiredness c) Enlarged spleen
3) Blastic phase	3-6 months	>30%	Increased blast cells in bone marrow only

1) Tyrosine kinase inhibitor resistance:

In the last several years, numerous anticancer agents have emerged on the market and one of the groups where they have increased research is TKIs. These TKIs can inhibit cell growth and tumour cell dissemination by specific and selective inhibition of distinct tyrosine kinases and thereby interfere with their respective cellular signalling pathways (13). Nevertheless, the advantage of TKIs as therapy was largely superseded by the emergence of multidrug resistance (MDR) associated with the over-expression of ABC membrane transporters (14). It is also noteworthy that some of these TKIs can potentiate classic chemotherapeutic drugs by overcoming ABC transporter and thus overcome the problem of MDR (15). BCR-ABL1 Tyrosine Kinase Inhibitors that are initiated by doctors have given outstanding results. However, some patients may still never respond (primary resistance) or may go into relapse following a response (secondary resistance). Some limited number of patients undergo the blastic phase (BP) which has a very poor prognosis phase once they develop resistance (16,17).

2) Imatinib in CML:

Imatinib (Gleevec, Glivec) is a synthetic agent used in the treatment of chronic myelogenous leukaemia and gastrointestinal stromal tumours (18). This agent is specifically made to block the breakpoint cluster region (BCR)-Abelson (ABL) fusion protein that leads from a chromosomal abnormality called the Philadelphia chromosome. This results in abnormalities of pubertal blood and the bone marrow with increased numbers of granular leucocytes- a feature characteristic of CML (19). To maximize efficacy, three second-generation agents (nilotinib, dasatinib, bosutinib) were approved as front-line therapy for CP CML after the approval of imatinib (20). These medicines demonstrate improved efficacy over imatinib against BCR-ABL1, including quicker cytogenetic and molecular remissions; but these improvements have not been associated with enhanced long-term results (21). Imatinib 400 mg is the most widely used dose of the drug, which is safe and effective, but, Imatinib 600 mg has also been widely researched as an option to improve the condition of CML patients (22,23).

3) Asciminib in CML (24):

Now, the activator-free BCR::ABL1 kinase inhibitor asciminib is approved for use in chronic-phase myeloid leukaemia patients who have failed 2 lines of therapy or are T315I positive (25). It is characterized by high specificity and significant potency against BCR: ABL1. By attaching to the myristoyl binding site, asciminib imitates the myristoylated N-terminus of ABL1. Hughes et al. (2019) reported that the allosteric inhibition of BCR-ABL1 kinase activity is reinstated upon binding (26). It is the first BCR-ABL1 inhibitor to selectively target the ABL myristoyl pocket (STAMP), which was optimized from the chemical structures of GNF-2 and -5, due to its distinct mechanism of action (27).The figure 1 below tells us about the classification of Tyrosine Kinase Inhibitor drugs:

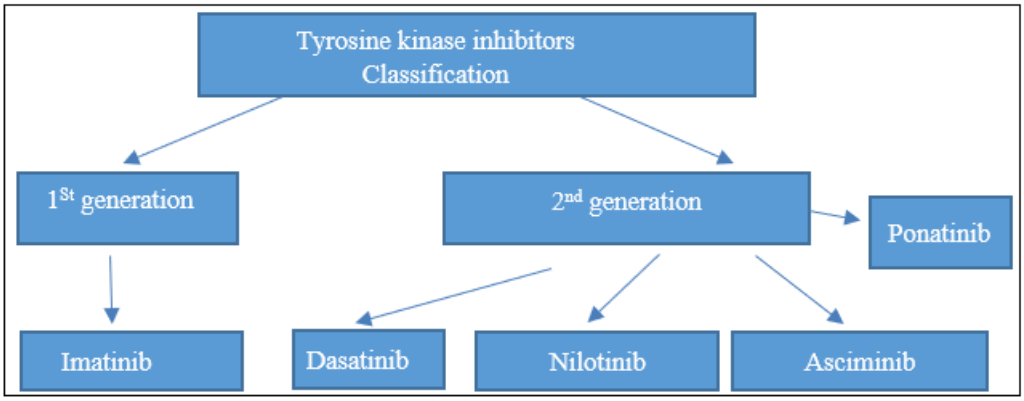

Figure 1

4) BCR-ABL mutational status:

Mutational analysis of *BCR::ABL1* kinase domain (KD) is a crucial component of clinical decision algorithms for chronic myeloid leukaemia (CML) patients, which is checked after failure or waning responses to tyrosine kinase inhibitor (TKI) therapy (28).

As therapy options become increasingly available for patients failing to achieve appropriate responses to imatinib, BCR-ABL KD mutation testing is becoming more useful to clinicians (29). The most common mechanism of resistance to tyrosine kinase inhibitor (TKI) therapy is represented by BCR-ABL1 kinase domain mutations, which are seen in 40–50% of patients with imatinib-resistant chronic myeloid leukaemia in the chronic phase (CML-CP) (4).

Patients with CML who are resistant to imatinib have been found to have more than 100 BCR-ABL1 single-point mutations (30). To test for BCR-ABL1 KD mutations, conventional Sanger sequencing is presently the recommended method. Due to its low sensitivity, Sanger sequencing cannot differentiate between compound and polyclonal alterations (31). Next-generation sequencing, or NGS, is becoming more and more common in diagnostic labs as a desirable substitute. The current body of knowledge regarding the clinical effects of NGS-based mutational testing in patients with CML precludes the recommendations with a high degree of certainty.

3. Conclusion

In this review article, we studied the effects of tyrosine kinase inhibitors on chronic myeloid leukaemia patients. Despite the wonderful outcomes made possible by the use of tyrosine kinase inhibitors, physicians must recognize that some patients may never respond (primary resistance), or helpful

responses may wane leading to relapse (secondary resistance). To maximize efficacy, three second-generation agents (nilotinib, dasatinib and bosutinib) have been approved as first-line therapy for CP CML after imatinib was approved. These agents appear to have improved efficacy vs imatinib for BCR-ABL1. BCR-ABL KD mutation testing is becoming more helpful to doctors as treatment alternatives for patients who do not respond appropriately to imatinib become more accessible. We recommend further research on these drugs in the treatment of Chronic Myeloid Leukaemia.

Ethical Statement

This narrative review was conducted in accordance with the highest ethical standards. The review synthesizes existing research, and as such, it does not involve any new human or animal subjects or require ethical approval. The review sourced all sources and studies from publicly accessible and reputable databases, and provided proper citations for all referenced materials. The authors affirm that they have conducted the review with integrity and transparency.

Conflicts of Interest:

The authors declare no conflict of interest.

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