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A REVIEW ON THE ROLE OF TYROSINE KINASE INHIBITORS AVAILABLE FOR THE MANAGEMENT OF CHRONIC MYELOID LEUKEMIA

Kaynat Fatima, Syed Tasleem Raza, Ale Eba, Sanchita Srivastava, Farzana Mahdi

Department of Biotechnology

Era's Lucknow Medical College & Hospital, Sarfarazganj Lucknow, U.P., India-226003

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Address for correspondence

Dr. Syed Tasleem Raza
Department of Biotechnology
Era's Lucknow Medical College & Hospital, Lucknow-226003
Email: tasleem24@gmail.com
Contact no: +91-8707038841

ABSTRACT

The function of protein kinases is to transfer a γ-phosphate group from ATP to serine, threonine, or tyrosine residues. Many of these kinases are linked to the initiation and development of human cancer. The recent development of small molecule kinase inhibitors for the treatment of different types of cancer in clinical therapy has proven successful. Significantly, after the G-protein-coupled receptors, protein kinases are the second most active category of drug targets. Imatinib mesylate was the first tyrosine kinase inhibitor (TKI), approved for chronic myeloid leukemia (CML) treatment. Imatinib induces appropriate responses in ~60% of patients; with ~20% discontinuing therapy due to sensitivity, and ~20% developing drug resistance. The introduction of newer TKIs such as, nilotinib, dasatinib, bosutinib, and ponatinib has provided patients with multiple options. Such agents are more active, have specific profiles of side effects and are more likely to reach the necessary milestones. First-line treatment decisions must be focused on CML risk, patient preferences and comorbidities. Given the excellent result, half of the patients eventually fail to seek first-line treatment (due to discomfort or resistance), with many of them needing a third or even further therapy lines. In the present review, we will address the role of tyrosine kinase inhibitors in therapy for chronic myeloid leukemia.

KEYWORDS: Chronic myeloid leukemia, BCR-ABL, Tyrosine kinase inhibitor, TKI, kinase domain.

INTRODUCTION

Chronic myeloid leukemia (CML) occurs due to genetic translocation in BCR-ABL gene in stem cells. The discovery of tyrosine kinase inhibitors (TKIs) has revolutionized CML therapy.

TKIs are highly effective for inducing remission, preventing disease progression and prolonging the survival of CML patients in chronic phase (CP) (1). Over the past two decades, the survival rate of chronic myeloid leukemia (CML) patient has increased in which patients will experience an almost normal life expectancy. Actually in clinical practice five TKIs are available for CML treatment. (2).While a proportion of patients (around 20 percent) will be able to successfully discontinue TKI therapy after a deep molecular remission is achieved, most of them will need to continue treatment (3). In this case, it is important for the physicians to be aware of which TKIs are appropriate for each unique clinical condition. (4) Furthermore, drawbacks of TKI treatment include (5) treatment failure in a subset of patients associated with insufficient response, disease progression and drug toxicity precluding drug administration, and (6) persistence of leukemia stem cells (LSCs) in the wider patient population, so that only a small proportion of patients may sustain treatment-free remission (TFR) after TKI therapy has been discontinued. Risks of prolonged TKI treatment include failure to comply with the risk of relapse and progression; toxicity, including severe vascular complications; and teratogenic effects. (7). By 2003, imatinib had been approved as a frontline therapy for CML, and since then, almost all patients with access to TKIs have received it as an initial treatment. Shortly afterward, second-generation drugs, including dasatinib, nilotinib, and bosutinib, were introduced with improved potency, various structures that allowed them to overcome most TKI-resistant mutations, and specific toxicity profiles, and eventually obtained regulatory approval. Dasatinib and nilotinib both TKIs were eventually compared with imatinib and typically showed higher response rates, with stronger and faster responses that were adequate to lead to their approval as initial therapy for patients with chronic phase CML (CML-CP). This rapid development resulted in the availability of multiple TKIs, and in addition, the concurrent use of different TKIs in CML-CP patients (8).

Table-1 illustrates the list of tyrosine kinase inhibitors.

TKI	Originally termed	TKI generation
Imatinib	STI571	First
Dasatinib	BMS-354825	Second
Nilotinib	AMN107	Second
Bosutinib	SKI-606	Second
Ponatinib	AP24534	Third

Table 1: List of tyrosine kinase inhibitors

REVIEW OF LITERATURE

Deregulated activity of the protein tyrosine kinase is central to the pathogenesis of human cancers. Targeted therapy in the form of selective tyrosine kinase inhibitors (TKIs) has transformed the treatment approach for different cancers and represents a therapeutic breakthrough. Imatinib was one of the first cancer therapies to demonstrate the potential for such targeted action. Imatinib, an oral targeted treatment, directly inhibits BCR-ABL, c-KIT, and PDGFRA(platelet-derived growth factor receptor A) tyrosine kinases. In addition to its remarkable success in CML and GIST(gastrointestinal stromal tumors), Imatinib benefits from numerous other tumors caused by PDGFR and c-KIT defects unique to Imatinib. Due to its anti-PDGFR action, imatinib has also been shown to be effective in steroid-refractory chronic graft-versus-host illness. Many studies represents an extensive review of Imatinib's role in oncology.

IMATINIB

Imatinib (also referred to as "Gleevec" or "Glivec"), a tyrosine kinase inhibitor, was dubbed a "magical bullet" when it revolutionized chronic myeloid leukemia (CML) treatment in 2001. Tyrosine kinases are important signaling cascade mediators which determine key roles in various biological processes such as development, differentiation, metabolism, and apoptosis in response to external and internal stimuli. Protein kinase deregulation activity has been shown to play a central role in the pathogenesis of human cancer. Imatinib, a derivative of 2-phenyl amino pyrimidine, is an inhibitor of tyrosine kinase with action against ABL, BCR-ABL, PDGFRA, and c-KIT. The active Tyrosine kinase sites each have an ATP binding site. The enzymatic operation catalyzed by tyrosine kinase is the conversion of the terminal phosphate on its substrates from ATP to tyrosine residues, a process known as protein tyrosine phosphorylation. Imatinib acts by binding near to the ATP binding site, trapping it in a closed or self-inhibited conformation, thereby semicompetitively inhibiting the protein's enzyme activity (9). Imatinib is well absorbed with 90% bioavailability(10). Imatinib is usually well tolerated after oral administration. Common side effects include fluid retention, headache, diarrhoea, appetite loss, weakness, nausea and vomiting, abdominal distention, oedema, rash, dizziness, and muscle cramps. Serious side effects could include defects in myelo suppression, heart failure and liver function (11).

The presence of a BCR-ABL fusion gene resulting from reciprocal translocation of chromosomes 9 to 22 (the Philadelphia (Ph) chromosome) is referred to as chronic myeloid leukaemia (CML). (12). BCR-ABL is the leukemogenesis driving factor at CML (13). The introduction of Imatinib, being a BCR-ABL inhibitor, quickly and significantly altered CML treatment and contributed to major improvements in management. (14). Some initial pioneering studies showed high rates of response to Imatinib in advanced CML patients (15) and those pretreated with (interferon-alpha) IFN-α (16). In a randomized trial, Imatinib was combined with the combination of (INF-α) and cytarabine in 1106 CP-CML patients (17). In 95.3% of patients, Imatinib induced complete haematological response (CHR) and in 73.8% of patients, complete cytogenetic response (CCR) was seen in some trials. Patients with imatinib have a higher quality of life (18). Imatinib received FDA approval based on these tests in December 2001. Imatinib mediated CHR in 98% of chronic-phase patients and CCR in 87% of 6-year follow-up patients in the IRIS (immune reconstitution inflammatory syndrome) trial. (19). Resistance to this agent occurs in some cases at an annual rate of approximately 4% in newly diagnosed CML, but more frequently in advanced form of diseases. Resistance, including BCR-ABL-dependent and BCR-ABL-independent mechanisms, can occur in many different ways. Kinase Domain point mutations in BCR-ABL gene are often connected with imatinib resistance. Such mutations impair the role of imatinib function, for instance by interfering with an imatinib binding site or by stabilizing a BCR-ABL conformation with reduced imatinib affinity (20, 21). BCR-ABL kinase domain mutations differ in how much they inhibit the binding of imatinib and cause resistance to this drug (22,23). Many approaches to get over imatinib resistance have been explored, including the development of new, more potent tyrosine kinase inhibitors (24).Examples of such inhibitors include nilotinib, (25) dasatinib, (26) and other clinically investigated TKIs such as bosutinib. clinical use of nilotinib has relatively weak potential to result in notable resistance development by Bcr-Abl-expressing cells. (27).

DASATINIB

Dasatinib is a potent BCR-ABL inhibitor. It is a second-generation, small-molecule, multi target kinase. This agent exerts greater activity in vitro against unmutated ABL kinase compared with imatinib. At first, Dasatinib was developed as a Src family inhibitor of kinases like Fyn, Yes, Src, and Lyk,

but it also inhibits BCR-ABL, EphA2, platelet-derived growth factor receptor, and c-kit. It also binds to other kinases of tyrosine and serine / threonine such as mitogen-activated protein kinases and receptor tyrosine kinase, discoidine domain receptor (28). Dasatinib may inhibit the propagation and kinase activity of imatinib-resistant wild-type and BCR-ABL mutant cell lines, except those carrying the T315I mutation. Studies in vivo have shown that dasatinib is 325 times more powerful than imatinib, and 16 times more potent than nilotinib (kinase inhibitor of BCR-ABL) against unmutated BCR-ABL (29).

Dasatinib binds to the ATP-binding position, but extends from imatinib in the opposite direction. Dasatinib binds to the inactive and active conformation of the ABL kinase domain, needs less ABL touch points, and has higher ABL kinase domain affiliation compared to imatinib. In vitro, dasatinib has shown greater than 325-fold activity against wild-type BCR-ABL, and the kinase activity of 14 of 15 BCR-ABL imatinib-resistant isoforms has been successfully inhibited at dasatinib nanomolar concentrations (30, 31). The effectiveness of dasatinib against multiple ABL kinase mutations is explained by the fact that interaction with some of the residues involved in these mutations does not require this. The ability of dasatinib against members of the Src family to inhibit kinase is greater (0.5 nmol/L) than its inhibitory activity against ABL (1 nmol/L). Dasatinib is delivered by mouth and ranges from 0.5 to 6 hours after oral administration. The half-life is 3-5 hours and absorption is not impaired by the consumption of food. Dasatinib is metabolised by cytochrome isozyme P450 (CYP) 3A44 (CYP) 3A44) into active and inactive metabolites. Thus, concomitant use of dasatinib with CYP3A4 inducers may decrease sensitivity to dasatinib, whereas toxicity of dasatinib may be increased by 3A4 enzyme inhibitors such as antiretrovirals, azole antifungals, and macrolides. Latest evidence indicates that orally administered dasatinib crosses the blood-brain barrier. Dasatinib concentrations found in cerebrospinal fluid in patients ranged from 1.4 to 20.1nM and were consistent with the antitumor activity of the central nervous system. (32).

NILOTINIB

Data from in vitro studies have shown that nilotinib is more potent than imatinib in inhibiting the activity of Bcr-Abl tyrosine kinase in cell lines and at least 10 to 30 times more potent than imatinib in inhibiting the proliferation of Bcr-Abl-expressing cells. Nilotinib's inhibition of cell growth has been associated with apoptosis induction, but the formation of normal human myeloid and erythroid progenitor cells are not affected at high concentration of nilotinib. In patients infected with imatinib resistance, nilotinib effectively blocked the proliferation of stably expressed Ba/F3 cell point mutations (E255V, F317L, M351 T, F486S, G250E, M244V, L248R, Q252H, Y253H, E255 K, E279 K, E282D, V289S, and L384 M). Nevertheless at concentrations of around 10 μM, the T315I mutant remained resistant to nilotinib. The autophosphorylation of the mutants E255 K, E255V, F317L, M351 T and F486S Bcr-Abl was also vigorously inhibited by nilotinib, and these findings were not associated with decreases in protein levels of Abl or Bcr-Abl. Overall, these results confirmed the conclusion that many imatinib-resistant Bcr-Abl mutants were comparatively or entirely more susceptible to nilotinib (33). In one study three hundred and twenty-one CML-treated patients (71% imatinib-resistant; 21% imatinib-intolerant) were evaluable. Nilotinib was administered twice daily at a dose of 400 mg on an empty stomach, and increased twice daily to 600 mg for inadequate responses. Full hematologic response was registered In 158 of 206 patients with active disease at the beginning (77 per cent). Overall, 57 percent of the main cytogenetic response rate was; 41 percent had full cytogenetic response. Large cytogenetic responses were observed in 125 (55 percent) of the 227 patients with imatinib resistance, and in 59 (63 percent) of the 94 patients with imatinib intolerance. The median time, respectively, for completing hematological response and main cytogenetic response was 1.0 and 2.8 months. For at least 18 months, the majority of patients (84 per cent) maintained the primary cytogenetic response. The overall survival rate was estimated at 91 per cent for 18 months. In another study, for a median period of 210 days 136 patients with accelerated phase CML received nilotinib at a dose of 400 mg twice daily. 28 In 69/129 patients (54 per cent), a confirmed hematological response occurred; 26 per cent had a complete hematological response. Major cytogenetic responses occurred in 40/129 patients (31 percent), with full cytogenetic responses in 24/129 patients (19 percent). Thirty out of 104 patients (29 percent) of patients immune to imatinib and 10/25 patients intolerant to imatinib (40 percent) had a strong cytogenetic response. First hematological response time and main cytogenetic response were 1 and 2.8 months, respectively. The estimated free and overall survival rates of 12-month progression were 57 percent and 81 percent respectively. Imatinib has helped a great many CML patients. But resistance to imatinib has emerged as a significant clinical challenge. Since imatinib therapy failed, novel treatment approaches were investigated. The availability of highly potent tyrosine kinase

inhibitors, such as nilotinib, has expanded the treatment approach. In patients with chronic, accelerated, and blastic phase CML, nilotinib tends to resolve resistance to imatinib, producing sustained cytogenetic and hematological responses in CML treatment. Although these have not yet been examined in clinical studies, combination strategies can be useful. Treatment options in CML are increasing with the availability of nilotinib and this is likely to continue in the future.

BOSUTINIB

Bosutinib tends to have a reasonably robust long-term efficacy in patients showing an initial reaction to advanced stage CML therapy, i.e., AP or BC. One research indicates that the long-term effectiveness and protection of the drug has been confirmed in advanced leukaemia patients in the Phase I / II trial. In this study, 79 AP patients, 64 BC patients, and 24 Philadelphia-chromosome-positive (Ph+) acute lymphocytic leukaemia (ALL) patients were treated with bosutinib. Most of these patients about 9% were highly pretreated, even with 3 TKI treatment lines. Long-term survival in this highly selected population of patients is still limited; however, sustained responses have been achieved particularly within the category of patients in AP. Median overall survival (OS) was not reached in this cohort with a median follow-up of 28.4 months (range0.3-88.6); 30 patients died, 11 of them within 30 days of their last dose of bosutinib. Few long-lasting responses were noted even among patients with Ph+ ALL, e.g. 1 patient sustained > 304.3 weeks of initial complete hematologic response (CHR) and 327 weeks of complete cytogenetic response (CCyR). In this case, Bosutinib appears to be similarly successful to that approved by other second-generation TKIs. E test 536 newly diagnosed patients with CP-CML were randomized 1:1 to receive 400 mg of bosutinib once daily (n=268) or imatinib (n=268).Median dose intensity for bosutinib was 392 and imatinib was 400 mg / d. For bosutinib vs imatinib, the MMR rate was notably higher at 12 months (47.2 percent vs. 36.9 percent; P=0.02). In addition, the CCyR rate was also remarkebly increased by 12 months (77.2 per cent vs. 66.4 per cent; P=0.0075). For patients treated with bosutinib the time to respond was much shorter within the 12-month follow-up period, only few patients in both arms (1.6 percent of bosutinib and 2.5 percent of imatinib patients) advanced to accelerated to blast level. While more patients discontinued treatment due to drug-related toxicity (12.7 percent for bosutinib and 8.7 percent for imatinib), for lack of efficacy or related reasons, this was outweighed in favor of bosutinib by a lower rate of discontinuations. Sadly, no randomized clinical trial comparing bosutinib with either dasatinib or nilotinib could be found. In a matching-adjusted indirect treatment, comparison of bosutinib, dasatinib, nilotinib, and ponatinib with respect to survival for second-line CP-CML, a favourable HR of 1.6 for PFS compared with nilotinib and dasatinib was described for bosutinib (34). These inter-trial comparisons are, however, somewhat contentious, and therefore need to be taken with extra caution and do not in any way substitute a direct comparison. Bosutinib is currently a well-established alternative therapy for patients with CML in the third and later lines of treatment. In patients with cardiovascular or respiratory diseases, most physicians might also find it in second-line treatment. The positive results of the first-line before trial could point to a possible use of the drug in first-line therapy in the near future.

PONATINIB

Ponatinib is a third-generation TKI, 520 times more active than imatinib, which inhibits both wild and mutant BCR-ABL1, including the T315I mutation resulting from threonine to isoleucine substitution at the position of 315 in ABL gene. The composition of Ponatinib may be subdivided into five major chemical units according to the interactions with the target oncoprotein. The hinge region consists of fused aromatic rings (imidazol-1, 2-pyridazine), which are capable of obtaining hydrogen bonds with the enzyme pocket and hydrophobic contact with the enzyme motif aspartate-phenylalanine-glycine(35). The ponatinib's second domain represents the principal distinction between ponatinib and other TKIs. In addition to the inability of first- and second-generation TKIs to create a hydrogen bond in T315I mutant leukemic cells for threonine replacement with isoleucine, isoleucine determines steric clash, blocking the TKI's access to the hydrophobic pocket but still allowing ATP to bind. Because dasatinib, bosutinib, and nilotinib need this hydrogen bonding to cause an anti-leukemic effect, ponatinib has a triple bond ethynyl linker that allows it to span the voluminous side chain of isoleucine. The triple bond also allows for a 10-fold increase in the potency compared to previous single or double-bonded molecules (36).Given ponatinib's pharmacokinetics, doses ranging from 15 to 60 mg cause proportional increases in peak plasma (Cmax) levels and the region under the concentration – time curve, but the drug's absolute bioavailability is still uncertain. Concentrations of Ponatinib plasma after a high-fat or low-fat meal aren't different when compared with fasting. A cancer center group compared the effectiveness and safety of ponatinib in pretreated CP-CML patients who received a low median daily dose (22.4 mg / day in 15 patients) and those treated with

CP-CML. Between the two groups no difference was found in the rate of MMR (p = 0.344) and MCyR (p = 0.625). Also, no difference in toxicity was observed with regard to adverse events of special interest (37). Role of ponatinib for TKI-resistant / intolerant or T315I-mutated CML The detection of T315I mutation in resistant CP-CML patients requires ponatinib treatment. Patients who have inherited this type of mutation will start ponatinib at full dose, modulating the initial dose according to the cardiovascular risk assessment standard and the level of response achieved. The growing concerns regarding arterial thrombosis, however, are likely to restrict the use of ponatinib. Ponatinib has an efficacy of cytogenetic and molecular responses in resistant or intolerant CP-CML patients to previous therapy lines but a risk-benefit assessment should always be considered in each case. Baseline factors such as age, comorbidity, disease status, mutational status, reason for therapy change (intolerance or resistance), cardiovascular risk, and previous therapy lines must be considered before starting with ponatinib in order to establish a safer initial dose. Low doses of ponatinib must always be treated in different subsets of patients according to the results obtained and the safety profile. In patients with a T315I mutation and a high baseline cardiovascular risk. In addition, there will be an increasing number of patients with T315I mutations who will be forced to stop ponatinib due to serious arterial complications and who are not transplant candidate.

CONCLUSION

Deregulation of kinases results in a variety of pathophysiological changes which cause the proliferation of cancer cells and metastasis. Kinase hyperactivation also enhances the anti-apoptotic effects. About one-third of all protein targets currently under research in the pharmaceutical industry are based on kinase. Kinase inhibitors are targeted treatment arising from the understanding of molecular genetics and mechanisms of molecular signaling. Most kinase inhibitors approved by the FDA target kinase enzyme binding site for ATP and give therapeutic indications against tumorigenesis. This medical class represents a change from traditional chemotherapy to targeted cancer treatment. Kinase inhibitors have solved a major drawback to current cancer treatment since it effectively discriminates between normal non-malignant cells and cancer cells that are rapidly proliferating. It leads to less of off-target effects in the cancer patient population and reduced toxicity. In conjunction with cytotoxic chemotherapy or radiation therapy, kinase inhibitors are often useful too. A critical threat to the therapeutic use of kinase inhibitors in the prevention of stem cells that are drug resistant to cancer. This phenomenon occurs to compensate for the loss of function of an essential kinase due to cellular strain. Dasatinib, nilotinib, and bosutinib are appropriate treatment choices for patients who continue to use imatinib. The second line treatment selection is based on the mutational status of the BCR-ABL kinase domain, the form of side effects associated with imatinib, and the comorbidities of the patient. Imatinib was the first approved TKI and is widely considered by most patients to be a very good front line alternative. The exciting opportunities are new TKIs with improved potencies and safety profiles, and drugs that work at alternative sites improving responses.

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