JIRCMS Vol.: 01 ll Issue 01 ll Page 01-57 ll April 2017

A Comprehensive Review of Alternative Inhibitors in Imatinib Resistance in Chronic Myeloid Leukemia

Murali Paramanandhan[1], Dr. Surendra Beniwal[2], Dr. H.S. Kumar[3], Dr. Rajesh Kumar[4], Dr. Ramesh Purohit[5]

1,4,5 Resident, 3 Senior Professor and HOD, Department of Radiation Oncology, 2Assistant professor, Department of Medical Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S P Medical College, Bikaner

Corresponding author:Dr. Murli Paramanandhan, Room No 38, PG Boys Hostel, Sardar Patel. Medical College & Associated Group of Hospitals, Bikaner, Rajasthan, India, 334001, Email: josh.messi19@gmail.com

ABSTRACT: The BCR-ABL mutation is present in CML, the development of point mutation along this domain leads to resistance to Imatinib. The advent of newer techniques like the Denaturing high performance liquid chromatography (DHPLC), direct sequencing and allele specific polymerase chain reaction (ASO-PCR) has helped in identify these mutations with greater accuracy. This article highlights the imatinib resistance, the best possible alternatives available in imatinib resistance.

KEYWORDS: Chronic myeloid leukemia, Imatinib resistance, kinase inhibitors.

INTRODUCTION:

Imatinib is a tyrosine kinase inhibitor (TKI) . The basic mechanism of imatinib is binding to inactive form of BCR-ABL tyrosine kinase, which prevents adenosine triphosphate (ATP) from binding.[1] The efficacy and safety of imatinib was confirmed by the IRIS study which compared the results of imatinib (Glivec) vs interferon. This study concluded that the patients treated with Imatinib showed good response in terms of complete cytogenetic response (83%) and overall survival rate (85%).[2] Achieving molecular and cytogenetic response reduces progression, relapse and death as per the European LeukaemiaNet (2014) (Table 1).[3]

TABLE: 1 Definition of suboptimal response and imatinib therapy failure according to the European LeukemiaNet[3].

Evaluation period	Suboptimal response	Failure to respond to imatinib
3 months	Absence of cytogenetic response (CgR)	Incomplete hematological response (HR)
6 months	CgR but less than partial CgR	Absence of CgR
12 months	Partial CgR (presence of 1-35% Ph+cells)	CgR but less than partial CgR
18 months	Molecular response (MR) but less than major MR (ratio of BCR-ABL/ABL < 0.1%, corresponding to a = 3 log reduction in BCR-ABL transcripts)	CgR but less than complete CgR
Anytime during treatment	Major MR loss; mutations still sensitive to imatinib	Complete HR loss; complete CgR loss; low-sensitivity of mutations to Imatinib; presence of chromosome abnormalities.

A few patients after attaining complete response with imatinib develop resistance. There are multiple mechanisms of resistance. The most

frequently encountered resistance pattern is mutations in the BCR- ABL kinase domain. The other mechanisms are gene mutation, amplification, multidrug resistance (P-glycoprotein) and incomplete inhibition.[4-5] Nearly 70 mutations are described in the literature available. The most common mutations are 15, seen in upto 85% of cases. They are as follows: T315I, E255K/V, Y253F/H, G250E, M351T, F359C/V, M244V, H396R/P, E355G, M237I, F317L, Q252H/R, L248V, D276G, F486S (TABLE: 2).[6]

Kinase domain mutations	Mutation-independent	Duplication	Other targets
T315I	PI3K/Akt	Amplification of ABL	P53
P-Loop M244V G250E Y253F/H E255K/V	HIF-1α		bcl-2
M351T	Aberrant ceramide metabolism		JAK2/STAT5
F359V	MDR-1		OCT 1
SH2, SH3	Pgp		
Cap			

It is recommended by the European LeukemiaNet that it is imperative to identify the mutation in patients showing suboptimal response or fails to respond to imatinib. Therefore, once the mutation is identified, the best possible alternative can be chosen for therapy.[3]

Denaturing high performance liquid chromatography (DHPLC), direct sequencing and allele specific polymerase chain reaction (ASO-PCR) are the recently introduced investigations to detect mutations. Direct sequencing is the gold standard technique for mutational assay. Sensitivity is 10-25% when compared to DHPLC 5-10% and ASO-PCR 0.1-1%.[3, 7-9]

Studies have revealed that there are inherent mutations that are present before beginning imatinib. The inhibition of tyrosine kinase leads to clonal selection and thereby increases the chances of identification by few sensitive detection assays. However, other mutations may be acquired during the therapy, progression of disease.[9-10] Sensitivity of the drug is defined as the concentration required to inhibit 50% of the wild type of BCR-ABL kinase in vitro (IC_{50}). Hence, it can be inferred that lesser the IC 50, more potent is the drug. The mutations are further classified as per the IC50 for every drug as sensitive, intermediately sensitive and insensitive.[11-16] A phenomenon of deselection has been described in a few studies. On discontinuation treatment, a proliferative disadvantage for the mutant can occur. In patients with T315I mutation, this phenomenon is rarely reported.[17]

The classifications of sensitivity of drugs based on in-vitro studies are not always accurate and clinical validation is required. If and when validated, it is a useful guide for definitive therapeutic intervention after treatment failure. In vivo there are many variables which is in the overall response in a patient. These issues are not addressed by in vitro studies.

Clinical response varies depending on the ethinicity, compliance, patient profile, interaction of drug in the body etc.[18] Therefore, the decision of choosing the best TKI is choice of a physician, but it should always be on the basis of mutational analysis, patient profile, stage of disease and other inherent co-morbidities of the patient.[19] This review article highlights the best possible TKI and other drugs under study to overcome imatinib resistance.

NOVEL BCR-ABL TYROSINE KINASE INHIBITORS:

Novel TKI include selective inhibitors, aurora kinase inhibitors and dual ABL/SRC kinase inhibitors.[20, 21]

BCR-ABL tyrosine kinase:

Tyrosine kinases are involved in the transduction pathways through the interaction of several oncoproteins. This fundamentally affects the cell proliferation, apoptosis etc. This is directly causes gene transcription and suppression. The proteins involved are the adapter proteins like the SRC kinase family, growth factor receptor-bound protein-2 (Grb2), focal adhesion kinases (FAK), growth factor receptor-binding protein complex (Gab2).[22]

There are multiple pathways involved in the signal transduction of the BCR-ABL. They are:

1. the RAt Sarcoma (RAS) pathway
2. Extracellular signal regulated kinase pathway (ERK)
3. Mitogen-activated protein kinase pathway (MAPK)
4. Phosphatidyl-inositol-3-kinase pathway (PI3K)
5. kB nuclear factor pathway (NFkB).
6. signal transduction and activator of transcription 5 (STAT5)

SRC kinase family

The SRC kinase proteins are involved in cell growth regulation through the signal transduction mechanism. Its is made of 9 homologous intracellular protein receptors. These are SRC, FYN, YES, BLK, YRK, HCK, LCK and LYN.[23] The BCR-ABL gene consists of SH3-SH2 region which contains multiple residues of tyrosine. These regions are phosphorylated by the SRC family mainly the HCK, LYN and FYN leading to increased activity. Imatinib resistance has be closely linked to HCK and LYN activation or overexpression during the progressive phase of the disease.[25-27]

Aurora kinase

The aurora kinase also called the serine/threonine kinase. This is essential in controlling the chromatid segregation of the daughter cells during cell division. It is classified into three classes: Aurora kinase A (AK-A), Aurora kinase B (AK-B), Aurora kinase C (AK-C). AK-A acts during prophase and is required for correct function of the centrosomes. AK-B attaches the mitotic spindle to the centromere. AK-C action is not known though it has been postulated to act on the germ-line cells.[28]

Dasatinib (Sprycel®, Bristol-Myers Squibb)

Dasatinib is a multi-target inhibitor. It inhibits the *BCR-ABL* tyrosine kinase, platelet-derived growth factor (PDGF), SRC family kinases and c-kit receptors. It acts on the adenosine triphosphate (ATP) binding site of ABL, regardless of the site activation state; it is 325 times more potent than the imatinib in respect to wild type *BCR-ABL* cells and has a much smaller IC50.[13,29,30] Mutations like L248, Y253, E255, F359, H396 are found to have high reponse rates whereas mutations like T315, F317 and V299 are associated with dasatinib resistance.[11]

Dasatinib is metabolized in the liver by cytochrome P450.[31] The indications of dasatinib are as a second-line treatment in patients with CML with resistance, poor responders, progression on imatinib. It can also be used as a first line therapy in CML patients presenting in the chronic phase. It is known to achieve rapid complete cytogenetic response (CCyR).[32,33]

Trails have shown that dasatanib show faster and a significantly higher cytogenetic and molecular response when compared to that of imatinib.[34]

Nilotinib (Tasigna®, Novartis)

Nilotinib is structurally similar to imatinib and its mechanism of action and efficacy is also similar to imatinib. In addition, it inhibits the PDGF and c-kit receptors. But it has a greater selectivity for *BCR-ABL*.[35,36]Nilotinib is found to be 20 times more potent than imatinib in wild BCR-ABL mutations. Smaller concentration of drug induces greater apoptosis. All patients respond well to nilotinib expect in mutations like E255K/V, F359C/V, Y253H and T315I.[12,13] it is also metabolized in the liver by the cytochrome P450. It does not use the organic cation transporters (OCT-1), and there is differences in the efflux patterns of the drug.[37]

The indications of nilotinib are as a second-line drug in the accelerated and chronic phases of CML, in patients intolerant or resistant to imatinib, minimal cross-intolerance to imatinib.[31,38] In nearly all patients started on nilotinib in the early phase of nilotinib have shown a faster and CCyR. The toxicity was also significantly low in these patients.[39]

In the phase II and III studies, comparison between nilotinib and imatinib have shown faster and more intense molecular and cytogenetic responses with more patients achieving undetectable levels of the disease. Only one patient in the study progressed to accelerated phase.[34]

Bosutinib (SKI-606, Wyeth)

Bosutinib was identified as a SRC inhibitor, but was later found to act on the BCR-ABL receptor. It has pro-apoptotic and anti-proliferative and pro-apoptotic agent of *BCR-ABL* cell lines. The mechanism is similar to dasatinib, but it does not inhibit PDGFR and EGFR.[40,41]

Lower concentrations of drug is required when compared to imatinib. It is also known to inhibit proteins with multi drug resistance at high concentrations.[41,42] Bosutinib is resistant to T315I and V299L in in vitro studies.[16]

It is currently in phase III trials. The phase II trials have shown that bosutinib is effective in patients with imatinib resistance and those intolerant to imatinib. Also used in patients with mutations within the kinase domain.[43]

Ponatinib (Iclusig)

Ponatinib is active in mutations involving the T315I mutation. It mainly acts via the inactive ABL sites was developed to interact with the inactive ABL conformation at multiple sites and with the T315I mutation, providing high affinity and efficacy.[44] It also inhibits PDGFRα, SRC family kinases and c-KIT, but not Aurora kinases.[44] This has cleared the phase I clinical trials. It was used in patients resistant to all the novel TKIs. 67 patient were included, achieved CCyR in 82% of patients with T315I mutations.[45]

Saracatinib (AZD0530, Astra-Zeneca)

Saracatinib acts as a dual kinase inhibitor. It has a selective action on the SRC/ABL kinases. Saracatinib overcomes the E255K and Y253F but not the T315I mutations. It is a matter of

debate on the inhibitor action.[47,48] Saracatinib has not entered clinical trials in CML. It has been tested in animal models with CML and in clinical trials in recurrent and metastatic squamous cell carcinoma of head and neck.[48,49]

INNO-46 (NS-187, Nippon-Shinyaku)

INNO-46 is a dual *BCR-ABL*/LYN tyrosine kinase inhibitor. It is 25-55 times more potent than imatinib regarding the *BCR-ABL* self-phosphorylation block. It also inhibits PDGFR and c-Kit receptor. In imatinib resistance disease, the progression can halted by the inhibition of LYN kinase. d Its sensitivity is lesser than imatinib in the mutations involving the ABL kinase regions. However, greater research is required to evaluate the drug in patients with TKI resistance.[27,50-52]

In the phase I studies, 56 patients were included. Most of them were either resistant or intolerant to TKIs. The dose was fixed at 240mg twice a day. Six patients showed a high CCyR. Inspite of high CCyR, the overall response is expected to be lower as it is used as a third line drug in the treatment of CML.[52]

Tozasertib (MK-0457)

Tozasertib was originally developed by Vertex Pharmaceutical as VX-680. In vitro studies in tumor cells have shown it to be an aurora kinase inhibitor, binding to 37 kinases and to mutant forms of imatinib resistance.[28,53] The phase II trials were suspended following the cardiac related toxicity in the form of QT interval prolongation.[54]

ON012380

ON012380 (Onconova) is a *BCR-ABL* inhibitor. It is found to be active against 100% resistant mutations to imatinib including the T315I mutation. It is a unique and a novel drug as it acts as a non-competitive ATP inhibitor of BCR-ABL. It holds promise in the treatment of imatinib resistant CML in the near future.[55] It is 10 times more potent than imatinib, may also be effective in cells with active or overexpressing the LYN kinases.[55,27]The safety and efficacy of the drug needs to be confirmed by clinical trials.[56]

CONCLUSION:

Imatinib is the most commonly used TKI. With the availability of newer TKIs, it is important that every patient undergoes mutation analysis as a guide in clinical decisions. This becomes all the more important in patients developing resistance to imatinib. Finally the choice of the ideal TKI should be based on the patient profile, status of the disease, co-morbidities along with mutation especially the T315I.

FOOTNOTES: Conflict of interest: The authors declare no competing financial interest

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