Imatinib resistance: a review of alternative inhibitors in chronic myeloid leukemia

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The development of point mutations in the BCR-ABL kinase domain is the main reason for imatinib resistance in chronic myeloid leukemia. Different detection methods are used in chronic myeloid leukemia monitoring, such as direct sequencing, denaturing high performance liquid chromatography and allele specific polymerase chain reaction. Mutation analysis has become mandatory during patient workup of chronic myeloid leukemia in order for the physician to choose the most suitable tyrosine kinase inhibitor. This article, a review of possible therapies used to overcome imatinib resistance, investigates the current position by searching the PubMed electronic database using the following keywords: imatinib, dasatinib, nilotinib, aurora kinase, SRC kinase, mutation, treatment, drugs and resistance. New tyrosine kinase inhibitors include BCR-ABL kinase selective inhibitors, dual ABL/SRC kinase inhibitors and aurora kinase inhibitors. Awareness of the spectrum of new drugs against mutations, in particular the T315I mutation, makes it possible to properly select the best therapy for each patient.

Keywords: *Leukemia, myelogenous, chronic, BCR-ABL positive/drug therapy; Protein-tyrosine kinases; Drug resistance, neoplasm; Antineoplastic agents/therapeutic use; Piperazines/therapeutic use; Pyrimidines/therapeutic use*

Introduction

The eight-year IRIS study, which compared the therapeutic results of interferon and imatinib (Glivec®), confirmed the effectiveness of imatinib and its long-term safety in chronic myeloid leukemia (CML).[1] Imatinib is a tyrosine-kinase inhibitor which binds to the inactive form of *BCR-ABL* tyrosine kinase, preventing adenosine triphosphate (ATP) from binding.[2]

The complete cytogenetic response for patients treated with imatinib as the first line drug is 83% and the overall survival rate is 85% as revealed in the eight-year IRIS study.[1] In addition, according to the European LeukemiaNet, achieving cytogenetic and molecular responses during the period reduces the risk of relapse, progression and death.[3]

Nonetheless, some patients develop resistance to imatinib even after attaining a response. Resistance mechanisms are heterogeneous and may involve *BCR-ABL* gene amplification, gene mutation, incomplete inhibition and overexpression of the multidrug resistance gene (P-glycoprotein) which may favor the selection of resistant cells. Resistance is commonly due to mutations within the *BCR-ABL* kinase domain.[4,5] More than seventy different amino acids substitutions in this domain have been described, but approximately 85% of all cases carry one of the following fifteen mutations: T315I, Y253F/H, E255K/V, M351T, G250E, F359C/V, H396R/P, M244V, E355G, F317L, M237I, Q252H/R, D276G, L248V, F486S.[6]

If the patient reaches a suboptimal response or fails to respond to imatinib, the European LeukemiaNet recommends mutation identification before changing with another tyrosine kinase inhibitor or to another therapy (Table 1).[3]

Different methods for mutation detection were introduced in CML handling, such as direct sequencing, denaturing high performance liquid chromatography (DHPLC) and allele specific polymerase chain reaction (ASO-PCR). Direct sequencing is the most used method; it is the gold standard in diagnostic routine, showing mutation detection sensitivity of 10-25% compared to DHPLC (5-10%) and ASO-PCR (0.1-1%).[3,7-9]

More sensitive detection methods have identified that some mutations pre-exist before imatinib treatment, but are normally detected after clonal selection following tyrosine-kinase inhibition, showing that the tyrosine kinase inhibitor has a selective

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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.

influence over the total cell population. Other mutations can be acquired during disease progression in association with genetic instability.[9,10] *In vitro* studies have identified mutations that can decrease tumor response to second generation tyrosine kinase inhibitors. Sensitivity is described by the concentration of drug necessary to inhibit 50% of wild type *BCR-ABL* tyrosine kinase (IC_{50}) *in vitro*, therefore, the smaller the IC50, the more powerful the drug is. Mutations are classified according to the IC_{50} of each tyrosine kinase inhibitor as sensitive, intermediately sensitive or insensitive.[11-16]

Some studies have described that after treatment discontinuity, a proliferative disadvantage for the mutant clone (deselection) can occur. This effect seems to be less frequent in patients with the T315I mutation compared to mutations in the phosphate loop region.[17]

In vitro sensitivity classifications are not completely accurate and need clinical validation. When validated, they are very useful to guide the proper therapeutic intervention after treatment failure. Furthermore, classification based on *in vitro* studies is not simple, since a particular mutation can be described as resistant or sensitive to the same inhibitor, for instance, the G250E mutation.[14]

In vitro studies do not take into account in vivo variables such as drug absorption, distribution, metabolism, transportation and excretion, which greatly influence the overall clinical response to therapy. Moreover, clinical response also varies from patient to patient, depending on treatment adherence, interaction with food and/or medicines, as well as genetic background.[18]

Therefore, mutation analysis becomes mandatory for the physician's decision in order to choose the most adequate tyrosine kinase inhibitor, always taking into consideration other factors such as disease stage, patient characteristics, risk factors and co-morbidities.[19]

This article, a review of possible therapies used to overcome imatinib resistance, investigates the current position by searching the PubMed electronic database using the following keywords: imatinib, dasatinib, nilotinib, aurora kinase, SRC kinase, mutation, treatment, drugs and resistance.

Novel *BCR-ABL* tyrosine kinase inhibitors

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

BCR-ABL tyrosine kinase

Tyrosine kinases participate in fundamental cell processes such as proliferation, adaptation and apoptosis through interactions with several proteins involved in oncogene signal transduction pathways, and are responsible for gene transcription activation or suppression. These interactions are mediated by adapter proteins such as the growth factor receptor-bound protein-2 (Grb2), growth factor receptor-binding protein complex (Gab2), SRC kinase family and focal adhesion kinases (FAK).[22]

The main pathways involved in *BCR-ABL* signal transduction are: the RAt Sarcoma (RAS) pathway, mitogen-activated protein kinase pathway (MAPK), extracellular signal regulated kinase pathway (ERK), phosphatidyl-inositol-3-kinase pathway (PI3K), signal transduction and activator of transcription 5 (STAT5) and kB nuclear factor pathway (NFkB).[22-24]

SRC kinase family

The SRC kinase family of proteins participates in signal transduction processes, contributing to cell growth regulation. This family structurally comprises nine homologous intracellular receptors (SRC, FYN, YES, BLK, YRK, HCK, LCK and LYN).[23] There are multiple tyrosine residues in SH3-SH2 regions of *BCR-ABL* that are phosphorylated by HCK, LYN and FYN kinases (SRC family), increasing their activity. During CML progression, LYN and HCK overexpressions and/or activation can occur, suggesting a relationship with imatinib resistance.[25-27]

Aurora kinase

The aurora kinase family is essential for mitotic progression. Aurora kinase A acts in the formation of the mitotic fuse and in the centromere maturation, allowing chromosome segregation into daughter cells. Aurora kinase B, in turn, is essential for the cytokinesis and aurora kinase C is mostly restricted to germinative cells.[28]

Dasatinib

Dasatinib (Sprycel®, Bristol-Myers Squibb) is a multi-target inhibitor of *BCR-ABL* tyrosine kinase, SRC family kinases, platelet-derived growth factor (PDGF) 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 powerful than the imatinib in respect to wild type *BCR-ABL* cells and has a much smaller IC50.[13,29,30]

High response rates to dasatinib have been observed in patients with L248, Y253, E255, F359, H396 mutations. In comparison, T315, F317 and V299 mutations are associated with dasatinib resistance.[11]

While imatinib is a P-glycoprotein substrate which is highly expressed in hematopoietic stem-cells, dasatinib is not.[31] Similar to imatinib, dasatinib is metabolized in the liver, mainly by cytochrome P450 and thus potentially presents drug interactions.[32] Dasatinib is approved for second-line treatment in patients with CML who were not successfully treated using imatinib. Moreover, dasatinib is effective as initial treatment of CML patients in the chronic phase, rapidly reaching complete cytogenetic response.[33,34]

Phase II and III studies on dasatinib showed faster and more prominent molecular and cytogenetic responses compared to imatinib.[35]

Nilotinib

Nilotinib (Tasigna®, Novartis) has an imatinib-derived structure. Therefore, nilotinib binds to a *BCR-ABL* inactive conformation, occupying the same site as ATP in the enzyme active conformation. It also inhibits the platelet-derived growth factor tyrosine kinase (PDGF) and c-kit receptors, showing an efficiency similar to imatinib and having a higher selectivity for *BCR-ABL*.[36,37]

In wild type *BCR-ABL* cells, nilotinib is 20 times more potent than imatinib, inducing apoptosis with significantly smaller concentrations compared to imatinib. Nilotinib is effective in patients with most mutations, except for E255K/V, F359C/V, Y253H and T315I mutations.[12,13]

Nilotinib presents differences in efflux patterns as it does not use organic cation transporters (OCT-1).[38] Similar to imatinib and dasatinib, nilotinib is metabolized in the liver, mainly by the cytochrome P450 and thus potentially presents drug interactions.[32]

Nilotinib is approved as a second-line treatment in the chronic and accelerated phases of CML, in CML patients resistant or intolerant to imatinib, minimal cross-intolerance to imatinib and in the presence of few adverse effects.[32,39] Nilotinib presents a fast and complete cytogenetic response in the initial chronic phase of almost all patients, with a low toxicity profile.[40]

Nilotinib phase II studies showed faster and more intense molecular and cytogenetic responses when compared to imatinib and only one patient in this study advanced to the accelerated or blastic phase. Phase III nilotinib studies showed greater molecular and cytogenetic responses and more patients reached undetectable levels of the disease.[35]

Bosutinib

Bosutinib (SKI-606, Wyeth), originally identified as a SRC inhibitor, is a potent anti-proliferative and pro-apoptotic agent of *BCR-ABL* cell lines. It is similar to dasatinib, but it does not inhibit growth factor tyrosine kinase receptors, such as PDGFR and epidermal growth factor receptor (EGFR). This feature may turn bosutinib less toxic than dasatinib, but a clinical comparison is necessary to confirm this.[41,42]

Tyrosine kinase inhibition by bosutinib was similar to that observed with imatinib, but demanding lower concentrations. At high concentrations bosutinib can inhibit the multiple drug-resistance protein, which has contributed to improved pharmacokinetic effects.[42,43] *In vitro* studies suggest that T315I and V299L mutations are resistant to bosutinib.[16]

In phase II trials, bosutinib was effective in patients who were resistant or intolerant to imatinib, including patients with mutations in the kinase domain. Currently, bosutinib is in phase III trials.[44]

Ponatinib

Ponatinib (AP24534) was developed to interact with the inactive ABL conformation at multiple sites and with the T315I mutation, providing high affinity and efficacy. Therefore, it also works against other imatinib-resistant mutations.[45]

Ponatinib has been shown to inhibit SRC family kinases, PDGFRα and c-KIT, but not Aurora kinases, which distinguishes it from other T315I inhibitors in development.[45]

In a phase I clinical trial ponatinib was used to treat 67 patients resistant to imatinib, dasatinib and nilotinib and passed safety requirements. Among these patients, 72% presented mutations in *BCR-ABL* at the beginning of the study or had a documented mutation story, including the T315I and F317L mutations. Moreover, 82% of patients were in the chronic phase, presented the T315I mutation and achieved a greater CgR.[46]

Saracatinib

Saracatinib (AZD0530, Astra-Zeneca) is a dual SRC/ABL kinase inhibitor. Saracatinib is able to overcome Y253F and E255K but not T315I mutations. If its inhibitory effect is a result of a direct effect on SRC, on ABL kinases or on both of them, is still a matter of debate.[47,48]

Saracatinib has been tested in CML animal models and in clinical trials for solid tumors such as recurrent or

metastatic head and neck squamous cell carcinoma. It has not entered CML clinical trials yet.[49,50]

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

INNO-46 (NS-187, Nippon-Shinyaku) is a potent dual *BCR-ABL*/LYN tyrosine kinase inhibitor. It is 25-55 times more powerful than imatinib regarding the *BCR-ABL* self-phosphorylation block. It also inhibits PDGFR and c-Kit receptor phosphorylation with a potency similar to imatinib. Studies suggest that LYN kinase inhibition can break the imatinib-resistant disease progression, being less sensitive to mutations in ABL kinase domain than other inhibitors, such as imatinib. However, it does not inhibit the T315I mutation and additional studies are needed to better evaluate the effectiveness of INNO-406 in patients who have developed resistance or intolerance to imatinib and to other tyrosine kinase inhibitors.[27,51-53]

In INNO-406 phase I studies, tolerance was for 240 mg doses twice a day and a high CgR was reached by six patients. From the 56 patients in the study, 71% were resistant and 29% were intolerant to imatinib, 26 patients were intolerant or resistant to dasatinib and 20 patients presented resistance or intolerance to nilotinib. Because it is a third-line treatment, a lower response rate is expected.[53]

MK-0457

MK-0457 (Merck, originally developed by Vertex Pharmaceutical as VX-680) is an aurora kinase inhibitor, which presents anti-proliferative and pro-apoptotic effects in a series of tumor cell lines.[28] It has been shown to bind to 37 of 119 tested kinases and to imatinib-resistant mutant forms.[54]

Different from imatinib, which binds deeply into the ABL kinase domain, MK-0457 is anchored by four hydrogen bridges, suggesting a mechanism for T315I mutation inhibition and an eventual clinical application.[55]

During MK-0457 phase I and phase II performance studies, important cardiac events, such as prolongation of the QT interval, were observed, causing additional MK-0457 trials to be cancelled and drug development was interrupted.[56]

ON012380

ON012380 (Onconova) is a *BCR-ABL* inhibitor, active against 100% of imatinib-resistant mutations including the T315I mutation. This is because ON012380 does not compete with ATP to inhibit *BCR-ABL*, but with its substrates suggesting that molecules with action sites out of the kinase domain can be good therapeutic agents against imatinib-resistant leukemias.[57]

In comparison to imatinib, ON012380 is 10 times more powerful. Besides being selective against *BCR-ABL*, it is likely that ON012380 is also effective against cells in which resistance to imatinib is due to overexpression or activation of LYN kinases.[57,27]

ON012380 has not entered clinical trials and so its effectiveness and safety in vivo have not been confirmed yet.[58]

Conclusion

Mutation analysis is important to guide clinical decisions regarding treatment, especially for patients who suspend imatinib due to intolerance or resistance. It would be ideal for all services to have access to mutation analysis tests before choosing the second or third tyrosine kinase inhibitors, since the identified mutation can influence the response to tyrosine kinase inhibitors. It is mandatory to know the action spectrum of new drugs against mutations, mainly T315I and to always take into account other variables involved in patient care, such as the individual characteristics of patients, clinical condition, comorbidities and treatment adaptation.

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