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Imatinib Therapy in Chronic Myeloid Leukemia: A Review

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ABSTRACT

The current aim for CML disease management in the TKI era is to provide age- and sex-matched normal life duration to CML patients. Despite the excellent outcome, many patients fail to treatment, with many of them requiring a third or even further lines of therapy. When selecting for such patients, it is essential to distinguish between failure and intolerance to previous TKIs To date more than 40 mutations have been identified and their early detection is important for clinical treatment. With the development of the new tyrosine kinase inhibitors (TKIs), associated with these mutations, the resistance problem seems to diminish, as some of the new drugs are less prone to resistance. The introduction of imatinib opened up different treatment perspectives in CML. For the patients resistant or intolerant to imatinib, second- and third-generation TKIs are successfully used in distinct CML disease states. TKI-related adverse events could impact the clinical course, especially in long-term drug administrations. The current article reviews the different aspects of imatinib therapy in CML patients.

Keywords: imatinib therapy, CML, Chronic myeloid leukemia

INTRODUCTION

Imatinib , marketed by Novartis as Gleevec (Canada, South Africa and the USA) or Glivec (Australia, Europe and Latin America), and sometimes referred to by its investigational name STI-571, is a tyrosine kinase inhibitor, designated chemically as 4-[(4-Methyl1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methane sulfonate.

Mechanism of action in CML

Imatinib mesylate is a 2-phenylaminopyrimidine derivative that functions as a specific inhibitor of a number of tyrosine kinase enzymes. It occupies the TK active site, leading to a decrease in activity. [1] There are a large number of TK enzymes in the body, including the insulin receptor. Imatinib is specific for the TK domain in abl (the Abelson proto-oncogene), c-kit and PDGF-R.BCR-ABL is a constitutively active tyrosine kinase, imatinib is used to decrease bcr-abl activity. The active sites of tyrosine kinases each have a binding site for ATP. The enzymatic activity catalysed by a tyrosine kinase is the transfer of the terminal phosphate from ATP to tyrosine residues on its substrates, a process known as protein phosphorylation. Imatinib works by binding close to the ATP binding site of bcr-abl, locking it in a closed or self-inhibited conformation, and therefore inhibiting the enzyme activity of the protein semi-competitively. [2]

This fact explains why many BCR-ABL mutations can cause resistance to imatinib by shifting its equilibrium towards the open or active conformation. [3] It is quite selective for bcr-abl.it also inhibits the abl protein of non-cancer cells but cells normally have additional redundant tyrosine kinases which allow them to continue to function even if abl tyrosine kinase is inhibited. Some tumor cells have a dependence on bcrabl. inhibition of the bcr-abl tyrosine kinase also stimulates its entry

into the nucleus, where it is unable to perform any of its normal anti-apoptotic functions.

Pharmacokinetics [4]

After oral administration, imatinib is rapidly and completely absorbed with an oral bioavailability of 98.3%, after which it is extensively metabolized, and up to 80% of the administered dose is recovered in the feces as metabolites or unchanged drug. The mean plasma half-life of imatinib is 13.5–18.2 h. Imatinib and its metabolites are excreted predominantly via the biliary-fecal route by the ATP-binding cassette (ABC) transporters, breast cancer resistance protein (BCRP) and P-glycoprotein. The main metabolite of imatinib, the N-desmethyl derivative CGP74588 (N-desmethyl imatinib), is formed in the liver by cytochrome P450 (CYP) 3A4, while a number of other enzymes, including CYP1A2, CYP2D6, CYP2C9 and CYP2C19, are involved in the formation of minor metabolites. CGP74588 accounts for approximately 20% of the plasma drug level in patients and has similar biological activity to the parent compound but a longer terminal half-life (85–95 h). [5]

Imatinib and CGP74588 are mainly glucuronidated to inactive O- and N-glucuronides by; however, the UDP-glucuronosyl transferase isoforms involved in the glucuronidation of imatinib have not yet been determined. These glucuronides are excreted into the bile, where they may be converted back to the parent drug and CGP74588 by bacterial -glucuronidases in the gut lumen. They are then reabsorbed through the process of enterohepatic recirculation, which is evidenced by a secondary plasma peak in the concentration time profile of imatinib and by the observation that there are conjugates present in the plasma and urine that are not detected in the feces[53]. However, the extent of the biliary excretion of imatinib glucuronic acid conjugates and their metabolites has not yet been reported. [6] The milk-plasma imatinib ratio after a daily oral administration of a 400-mg dose reaches 0.5 for imatinib and 0.9 for CGP74588.

TRANSPORT AND METABOLISM OF IMATINIB

After oral administration, imatinib is absorbed and interacts slightly with P-glycoprotein (P-gp) at the membrane of intestinal epithelial cells and is then transported to the intestinal lumen. Upon reaching the liver, imatinib is transported into hepatocytes by organic cation transporter 1 (OCT1), where it may undergo metabolism to N-desmethyl imatinib by hepatic cytochrome P450 (CYP) 3A4. A portion of the imatinib and N-desmethylimatinib is then glucuronidated to O- or N-glucuronides by UDP-glucuronosyl transferases. [7] Transport out of the hepatocytes into the bile occurs via breast cancer resistance protein (BCRP), which is located at the hepatocyte apical membrane. Imatinib and N-desmethyl imatinib glucuronides are excreted into the bile and may undergo enterohepatic recirculation and reconversion to imatinib and N-desmethyl imatinib by colonic bacterial glucuronidases. The oral bioavailability of imatinib is 98.3%.

IMATINIB RESISTANCE

Resistance to imatinib encompasses failure to reach CHR, CCyR, and MMR within an allocated duration of time (primary resistance). A number of patients still do not succeed in obtaining a CHR, 20 to 25% do not achieve a CCyR, and fewer than 10% of patients achieve complete molecular response (CMR). [8] Loss of a previously obtained response to imatinib (secondary or acquired resistance) occurs in some 20 to 25% of patients that reach CHR and/or CCyR[57].Further work on both primary cells as well as resistant cell lines identified a number of mechanisms by which resistance to imatinib arises, which are discussed below:

Oral Bioavailability

Imatinib is an oral medication and influenced by the adherence or compliance of the patient to imatinib therapy. Following ingestion, imatinib undergoes

gastrointestinal absorption and firstpass metabolism. Imatinib is highly plasma protein bound and is affected by drug influx and drug efflux transporter mechanisms. [9] Imatinib is metabolised through the cytochrome p450 system, with the isoenzyme CYP3A4 mainly implicated. Intrinsic variability of CYP enzyme activity and co-medication that may influence CYP3A4 isoenzyme activity can also contribute to the variability in imatinib concentrations.. However, no apparent difference in the frequency of dose-escalation was observed between the extremes of PK values, and at the present moment, the role of imatinib plasma levels remains exploratory and yet to be fully defined in clinical practice.

Plasma-protein Binding

Imatinib is approximately 95% bound to plasma proteins, mainly to albumin, as well as α-1 acidglycoprotein (AGP), a hepatic acute-phase protein. It was proposed that AGP can bind to imatinib in the plasma and hence decrease the availability of free or active drug, but studies have not confirmed the AGP binding as a mechanism for imatinib resistance, regardless of the dose of imatinib, and currently the influence of AGP as a cause of imatinib resistance remains doubtful. [10]

Intracellular Availability of TKIs

Multidrug efflux transporters of the ATP-binding cassette (ABC) transporter family, which include the multidrug resistance gene product P-glycoprotein (P-gp; ABCB1), and the breast cancer resistance protein (ABCG2), may have a significant effect on restricting drug uptake from tumor cells through active efflux. In addition to high expression on hematopoietic primitive cells, both ABCB1 and ABCG2 show tissue localization in the small bowel, brain, testes, and canalicular membrane of hepatocytes and may contribute to imatinib resistance by causing drug efflux from cells from these sites. [11] The ABCB1 transporter or MDR-1 is overexpressed in cells from patients in blast phase and implicated both in the reduced efficacy of chemotherapy in advanced-phase disease, as well as resistance to imatinib. The significance of the role of ABCB1 in imatinib resistance has yet to be fully clarified, as the efflux of imatinib from ABCB1-expressing cells is less pronounced than the efflux of cytotoxic drugs.

OCT-1

The human organic cation transporter (hOCT-1; SLC22A1) has been advocated as a significant factor affecting intracellular drug availability through inhibition of imatinib influx, and polymorphisms of OCT-1 may alter the entry of imatinib into cells through this transporter mechanism. Examining drug influx and drug efflux properties at presentation prior to therapeutic intervention, may give insight from the start of therapy about an expected response and potentially provide a strategy for the use of a particular TKI in order to achieve the best outcome for an individual patient. [12]

Clonal Evolution

Chromosomal abnormalities in the Ph+ population following presentation, defined as clonal evolution, usually indicate transformation to a more advanced phase and are shown in up to 80% of patients. The most common cytogenetic aberrations include, in order, an additional Ph+ chromosome, trisomy 8, and isochromosome17q. Clonal evolution is associated with a reduced response to imatinib with regard to cytogenetic response, increased hematologicalrelapse, and subsequent reduction in overall survival, and is proposed to reflect the genetic instability of the highly proliferative CML progenitors associated with CML progression. [13]

SRC Overexpression

SRC-family kinases play a pivotal role in signaling through surface receptors on hematopoietic cells, and of the nine members of the SRC family, HCK, FGR, and LYN are primarily expressed on myeloid cells and can also be activated by BCR-ABL1 kinase. Imatinib resistance and progression to, in particular, lymphoid blast

phase has been suggested to be mediated through LYN and HCK upregulation .Imatinib-resistant cell lines have shown greatly increased expression of LYN, which were susceptible to apoptosis following treatment with a SRC inhibitor. SRC-family kinases are also implicated in imatinib resistance by virtue of stabilizing the active conformation of BCR-ABL1 to which imatinib is unable to bind. [14]

Quiescent Stem Cells

Despite the remarkable results obtained with imatinib, disease persistence is detected in the majority of patients. The failure of imatinib to eradicate all malignant cells may be as a consequence of the inherent insensitivity of quiescent CML cells to imatinib. These primitive leukemic CD34+CD38- cells, which have entered the G0-phase of the cell cycle and are therefore quiescent, account for less than 1% of total CD34+ cells present at diagnosis , and it is this quiescent fraction that is postulated to sustain the disease with the constant potential to escalate. [15] The resistance of quiescent stem cells (QSC) seems multifactorial and includes altered drug influx or efflux mechanisms (a marked reduction in the expression OCT1 and an elevated expression of ABCB1 and ABCG2), increased BCR-ABL1 transcript levels in the absence of BCR-ABL1 gene amplification, and decreased BCRABL1 transcript degradation. Imatinib has recently been found to restore CXCR4 expression, recognized to be associated with cell migration defects in CML and down-regulated by BCRABL1 overexpression, thereby promoting the migration of CML cells to bone marrow stroma, causing G0-G1 cell cycle arrest and preserving the survival of quiescent CML progenitor cells. Residual disease is commonly observed in most patients, and QSC are present in inadequate numbers to account for this level of detection.

Increased Expression of BCR-ABL1

Amplification of BCR-ABL1 occurs more commonly in advanced-phase disease and was first reported in 3 of 11 patients with blast phase CML or Ph+ acute lymphoblastic leukemia who developed acquired resistance to imatinib. It is unclear whether these findings are as a direct result of increased expression of the BCR-ABL1 protein, or as a result of other factors implicated in transformation and imatinib resistance, such as point mutations in the ABL-kinase domain as documented in one of the three cases, or as a consequence of increased genomic instability. [16] However, in a subsequent study of 66 imatinib resistant patients, only 2 patients showed BCRABL1 gene amplification and overexpression of BCR-ABL1 is understood to account only for the minority of cases of imatinib resistance. Still, it would seem that the level of BCR-ABL1 protein is closely associated with the pace of the emergence of imatinib-resistant mutant subclones. Cells expressing a high level of BCR-ABL1 have been observed to be far less sensitive to imatinib and more rapidly yield imatinib-resistant mutant subclones than cells with low BCR-ABL1 expression levels.

ABL Kinase Domain Mutations

The emergence of mutations within the kinase domain of BCR-ABL1 is regularly associated with resistance to TKI therapy. The most frequently described mechanism of acquired resistance to imatinib is the occurrence of point mutations, representing a single aa substitution in the kinase domain, which impair drug binding by affecting essential residues for direct contact with the TKI or by preventing BCR-ABL1 from assuming the inactive conformation appropriate for imatinib binding. The published incidence of mutations remains variable and in the order of 40 to 90% as a consequence of different methods of detection, nature of resistance, and disease phase examined. [17]

Four categories of mutations have been recognized to correlate with clinical resistance to imatinib affecting the: (i) imatinib binding site, (ii) P-loop (ATP binding site), (iii) catalytic (C) domain, and (iv) activation (A) loop (2). Mutations in the phosphate (P-loop; residues 244-255 of

ABL), which account for up to 48% of all mutations in imatinib resistant cases, destabilize the conformation required for imatinib binding, and have been associated with an increased transforming potential and a worse prognosis regardless of their sensitivity to imatinib. P-loop mutations have been reported to be associated with a worse prognosis in comparison with other categories of mutations. [18] A series of mutations are located in the catalytic domain (residues 350-363 of ABL) and can also affect imatinib binding. The activation loop of the ABL kinase is the major regulatory component of the kinase domain and can adopt an open and/or active or closed and/ or inactive conformation. Mutations in the activation loop instigate the open and/or active configuration, and as the inactive and/or closed configuration is required for imatinib activity, resistance occurs. Nevertheless, aa substitutions at only seven residues [M244V, G250E, Y253F/H, E255K/V (P-loop), T315I (imatinib binding site), M351T, and F359V (catalytic domain)] account for 85% of all resistance associated mutations.

Although point mutations have been more frequently described in TKI resistance and advanced phase CML, they have also been documented prior to TKI therapy, inherently suggesting that pre-existing mutations do not acquire a survival advantage until subjected to a TKI. [19]

TABLE 1 :CLASSIFICATION OF TKI RESISTANCE

BCR-ABL1 INDEPENDENT	BCR-ABL1 DEPENDANT
Patient related Poor compliance **Pharmacological** Poor intestinal absorption Drug interactions Binding with plasma components **Leukemia cell related** Heterogeneity of CML cells - Reduced levels of transporter (hoct1) Increased levels of exporter (ABCB1, ABCG2) **QSCs** **Clonal evolution** **SRC overexpression**	**Increased expression of BCR-ABL1** Mutations in the ABL-kinase domain

RESPONSE CRITERIA

Response to imatinib treatment is measured in terms of hematologic, cytogenetic, and molecular parameters, as proposed by the European leukemia Net (ELN).[5]

TABLE 2 : CRITERIA FOR RESPONSE TO IMATINIB

Complete Hematologic Response (CHR)	Platelets < 450 $x10^9$/L, AND White cells < 10 $x10^9$/L, AND No circulating immature myeloid cells, AND < 5% basophils on differential, AND No palpable splenomegaly
Partial Cytogenetic Response (PCyR)	1 - 35% Ph+ cells
Complete Cytogenetic Response (CCyR)	No Ph+ cells ; fewer than 1 out of 200 nuclei BCR-ABL1–positive by FISH
Major Molecular Response (MMR)	BCR-ABL ≤ 0.10%
MR4.0	BCR-ABL < 0.01%
MR4.5	BCR-ABL< 0.0032%
Molecularly undetectable leukemia	BCR-ABL transcripts non-quantifiable and non-detectable

TABLE 3 :DEFINITION OF RESPONSE TO TREATMENT TO TKI AS FIRST LINE THERAPY

	Optimal	**warning**	**failure**
baseline	NA	High risk or CCA/Ph+, major route	NA
3 months	BCR-ABL1≤ 10 % and/or Ph+≤ 35 %	BCR-ABL1≥ 10 % and/or Ph+36-95 %	Non-CHR and/or Ph+>95%
6 months	BCR-ABL1<1% and/or Ph+ 0	BCR-ABL1 1-10% and/or Ph+ 1-35%	BCR-ABL1 >10% and/or Ph+ >35%
12 months	BCR-ABL1 ≤ 0.1 %	BCR-ABL1 >0.1-1%	BCR-ABL1 >1% and/or Ph+ >0
Then , and at any time	BCR-ABL1 ≤0.1%	CCA/Ph– (–7, or 7q–)	Loss of CHR,Loss of CCyR,Confirmed loss of MMR,Mutations CCA/Ph+

DISCUSSION

Decisions regarding first line treatment must be based on CML risk, comorbidities, and patients expectations. Despite the excellent outcome, half of the patients will eventually fail (due to intolerance or resistance) to first line treatment, with many of them requiring a third or even further lines of therapy. When selecting for such patients, it is essential to distinguish between failure and intolerance to previous TKIs. [20] In the present review, we will address all these issues from a practical point of view. To date more than 40 mutations have been identified and their early detection is important for clinical treatment. With the development of the new tyrosine kinase inhibitors (TKIs), associated with these mutations, the resistance problem seems to diminish, as some of the new drugs are less prone to resistance.

CONCLUSION

The introduction of imatinib opened up different treatment perspectives in CML. For the patients resistant or intolerant to imatinib, second- and third-generation TKIs are successfully used in distinct CML disease states. TKI-related adverse events could impact the clinical course, especially in long-term drug administrations. The current aim for CML disease management in the TKI era is to provide age- and sex-matched normal life duration to CML patients.

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