Monitoring imatinib plasma concentrations in chronic myeloid leukemia

Darlize Hübner Martins[1]

Sandrine Comparsi Wagner[1]

Tamyris Vianna dos Santos[1]

Lilian de Lima Feltraco Lizot[1]

Marina Venzon Antunes[1]

Marcelo Capra[2]

Rafael Linden[1]

[1]Universidade Feevale,
Novo Hamburgo, RS, Brazil

[2]Hospital Nossa Senhora da
Conceição, Porto Alegre, RS, Brazil

Imatinib has proved to be effective in the treatment of chronic myeloid leukemia, but plasma levels above 1,000 ng/mL must be achieved to optimize activity. Therapeutic drug monitoring of imatinib is useful for patients that do not present clinical response. There are several analytical methods to measure imatinib in biosamples, which are mainly based on liquid chromatography with mass spectrometric or diode array spectrophotometric detection. The former is preferred due to its lower cost and wider availability. The present manuscript presents a review of the clinical and analytical aspects of the therapeutic drug monitoring of imatinib in the treatment of chronic myeloid leukemia. The review includes references published over the last 10 years. There is evidence that the monitoring of plasmatic levels of imatinib is an useful alternative, especially considering the wide pharmacokinetic variability of this drug.

Introduction

The Brazilian National Cancer Institute (INCA) estimates that there were 9850 new cases of leukemia in Brazil in 2010 noting that in 2008 there were 5686 deaths in the country due to leukemia.[1] Chronic myeloid leukemia (CML) has an incidence of one to two cases per 100,000 per year and accounts for about 15% to 20% of all cases of leukemia.[2,3]

CML occurs mostly in adults, Caucasians, men and in the fourth and fifth decades of life.[2,4] CML has a clone origin and is characterized as a proliferation disorder of primitive myeloid cells, which starts to occur excessively in the bone marrow and causes cytogenetic and molecular alterations.[4,5] The anomalous chromosome formed by a reciprocal translocation between chromosome 9 and 22, t(9;22)(q34;q11), known as the Philadelphia (Ph) chromosome, is responsible for producing a hybrid protein called bcr-abl which has increased tyrosine kinase activity.

The presence of this chromosome is a maker for CML since it is present in more than 90% of the cases of this disease.[2-4,6] CML evolves through three phases: chronic (CP), accelerated (AP) and blastic phase (BC). CML almost always has a fatal evolution since it is difficult to achieve the elimination of the leukemic clone (Ph) with chemotherapy.[7] Treatment for CML includes drugs such as hydroxyurea, interferon-α (IFN-α) and imatinib mesylate (IM) and allogeneic bone marrow transplantation (BMT).[7,8] Allogeneic BMT is considered the only curative treatment for CML, with a 65% chance of cure.[9,10] However, only 15% to 30% of the patients can be submitted to transplantation due to the lack of histocompatible donors and the advanced age of the patients who are usually affected by the disease.

The immediate or delayed risk of serious complications also make this procedure less successful. Relapse rates after transplantation are between 5% to 30% in the CP, 60% in the AP and 90% in the BC.[3,6,11] Therefore, approximately only 20% of CML patients will be effectively cured by bone marrow transplantation.[10]

In the 1990s, 500 specific target molecules for CML treatment were studied, especially tyrosine kinase inhibitor drugs; the first representative to be launched was imatinib mesylate (IM), also known as STI-571, the symbol of the drug during its development, Gleevec® or Glevec®, the trade name of the drug manufactured by Novartis. IM is considered to be the first-line drug treatment for CML.[3,5,12] The drug dose is modified according to the stage of the disease.[5] The clinical protocol and the therapeutic guidelines of adult treatment advocate the use of 400 mg/day for CP and 600 mg/day for AP and BC.[8] The treatment for CML aims to obtain a hematological response followed by a cytogenetic response, based on myelosuppressive chemotherapy. The hematological response is characterized by a

reduction in the absolute count of leukocytes, elimination of immature myeloid cells from the peripheral blood and eradication of signs and symptoms of the disease. The cytogenetic response is defined as a reduction or even elimination of the Ph⁺ chromosome.[6,10,12] Recently diagnosed patients in chronic phase who received imatinib as a first-line treatment over 60 months achieved a high rate of hematologic response (98%), a complete cytogenetic response (CCR) of around 87% and an overall survival rate of 89%.[13] Currently second-generation tyrosine kinase inhibitors such as dasatinib and nilotinib are available; these are indicated in patients resistant to imatinib.[12]

Despite of the initial recommendation of a standard dosage of imatinib, several studies have identified a relationship between plasma drug levels and efficacy of treatment. Imatinib plasma concentrations outside the recommended therapeutic levels may be related to absorption variations, biotransformation or elimination due to genetic and environmental factors, interactions with other drugs or associated to lack of patient adherence.[9,14,15] Considering the positive impact of the therapeutic monitoring of imatinib in the treatment of CML, it is necessary to know the clinical aspects of imatinib pharmacokinetics as well as to establish monitoring of plasma levels in patients with CML. This study aims to review the clinical and laboratory aspects of therapeutic monitoring of imatinib in Ph⁺ CML patients.

Methods

This study was conducted in the form of a literature review on the clinical and laboratory aspects of monitoring imatinib plasma levels in Ph⁺ CML. An investigation was performed using keywords to search electronic databases such as Medline®, PubMed Central® and the Scielo Brazil Collection. Additionally websites related to this issue were accessed, including INCA, the Brazilian Ministry of Health and European Treatment Outcome Study (EUTOS). The survey was conducted in English and Portuguese using the following keywords, both individually and combined: chronic myeloid leukemia, imatinib, pharmacokinetic, therapeutic drug monitoring (TDM) and chromatography. The selection criteria of publications were: their topic and relation to the aim of this study, as well as their availability, publication date and scientific qualification of the journals in the Qualis system, if applicable. Publications from 2000 were selected as were previous studies, but only if they represented current data.

Pharmacodynamics and pharmacokinetics of imatinib

IM is a 2-phenylaminopyrimidine class drug, selective inhibitor of bcr-abl tyrosine kinase, acting specifically in the energy blockage for the tyrosine kinase domain of abl.[10,12] IM is also able to inhibit other signaling proteins like the platelet-derived growth factor receptor (PDGFR) and c-Kit.[12,16] IM binds to inactive tyrosine kinase bcr-abl, preventing it from attaching to adenosine triphosphate (ATP) and becoming active.[5,12] Thus, it prevents the proliferation of CML progenitor cells by blocking signaling pathways which were activated by this oncogene and reducing hematologic and cytogenetic involvement of CML.[7]

IM is mostly metabolized by the hepatic cytochrome P450 enzyme system; mainly CYP3A4 and CYP3A5 which exhibit widely variable activity among different individuals.[14] Metabolic processes include N-demethylation with formation of norimatinibe (CGP74588), oxidation of the piperazine ring with the formation of lactam derivatives and hydroxylation of the benzyl grouping. The oxidative metabolism is the main mechanism of clearance. Norimatinib is the main metabolite of IM; it has a similar biological activity to the drug,[14,17] and represents approximately 20% of plasma levels of the original drug.[14]

IM and its metabolites have predominantly biliary-fecal excretion. Excretion is slow with an average recovery of 80% within seven days (67% in feces, 13% in urine). Approximately 28% and 13% of the dose excreted correspond to imatinib and norimatinib, respectively.[17]

IM has a high intrinsic permeability and rapid dissolution in acid, allowing rapid oral absorption in humans.[18] In addition, 89% to 96% of IM is bound to proteins, leaving a small fraction of free drug in plasma.[18,19] The pharmacokinetic characteristics of IM are favorable, including rapid and complete oral bioavailability (98%) and the proportionality between exposure and dose. Its half-life is approximately 20 hours, allowing administration of a single daily dose.[14]

In 2004, Peng et al.[18] performed a study involving 64 patients with CML. After oral administration, the mean t_{max} was 4.2 hours, with detection of IM in plasma 30 minutes after taking the medicine. The terminal half-life in plasma of IM was 15 hours, and clearance was approximately 12.5 L/h at a dose of 400 mg.

The authors concluded that exposure to IM was dose-proportional after oral administration in a dose range from 25 to 1000 mg. There was an accumulation of the drug from 1.5 to 3 times at a steady state following administration of a single daily dose. The analysis of the pharmacokinetics/pharmacodynamics relationship indicates that the initial hematological response depends on the dose administered to the patients, a dose of 400 mg or more is required for maximum effect.

One of the largest studies on the use of imatinib in CML was the International Randomized Study of Interferon and STI571 (IRIS), which lasted for five years. In this trial, 31% of patients (171 of 553 patients) receiving imatinib discontinued the first-line treatment, 4% due to adverse events (AEs), 11% due to unsatisfactory therapeutic effect and 2.5% to switch to IFN-α treatment noting that primary resistance of patients in the chronic phase was 3%.[20]

Most patients who use the drug present with AEs, but these are usually mild to moderate.[14,17] The emergence of

AEs may be more dependent on the stage of disease or indicative of a slow response to therapy than a consequence of the plasma concentration of the drug.[14]

The AEs most commonly reported by Druker et al.[13] were edema (including peripheral and periorbital edema) (60%), pain, nausea (50%), muscle cramps (49%), musculoskeletal involvement (47%), diarrhea (45%), rash and other skin problems (40%), fatigue (39%), abdominal pain (37%), headache (37%) and joint pain (31%).

Grade 3 or 4 AEs consisted of neutropenia (17%), thrombocytopenia (9%), elevated liver enzymes (5%), anemia (4%) and other AEs related to the drug (17%). According to Deininger et al.,[21] the rate of treatment discontinuation due to toxicity is less than 5%; this is lower in patients who are at less advanced stages of disease. Variations in plasma clearance may result in toxicity or sub-optimal response. The toxicity of imatinib is often related to the dose.

Imatinib is subject to numerous pharmacokinetic interactions. Concomitant administration of drugs that induce CYP3A4 may lead to low and inefficient levels of imatinib.[18] Some substances that may reduce blood levels of imatinib include phenytoin, barbiturates, carbamazepine, dexamethasone, progesterone, rifampicin and hypericin. Moreover, imatinib plasma levels may be increased by concomitant use of aprepitant, clarithromycin/erythromycin, ciclosporin, itraconazole, grapefruit juice and pimozide.[21,22]

Some patients develop imatinib resistance, progressing to refractory treatment (primary resistance) or loss of sensitivity over time and relapse (secondary resistance).[16] Several mechanisms may cause this resistance, with some already known.[5,10,12] Resistance to imatinib can be multifactorial, presenting problems in the drug pharmacokinetics, mediators of cellular drug uptake, like the human organic cation transporter 1 (hOCT1) protein and mutations. Mutations are more frequent in secondary rather than primary resistance,[9] with the most common being deletion of BCR-ABL by amplification of this oncogene, mutation of the binding site of BCR-ABL by altered metabolism of imatinib, and by a transport mechanism.[5,10,12] Since 2001 with the first report of a mutation in resistant patients, more than 70 others have been reported. These mutations result in altered proteins many of which have prognostic significance.[9]

Therapeutic monitoring of imatinib

TDM has demonstrated to be useful for many therapeutic agents especially those that have a narrow therapeutic window or large pharmacokinetic variability among patients. It has been used in antineoplastic chemotherapy when the relationship between exposure and the pharmacokinetics of the clinical response has been established.[23] Titier et al.[24] found a high interindividual variability of plasma concentration in imatinib therapy, with coefficient of variation of 50% for doses of 400 mg/day and of 45% for 600 mg/day.

The evaluation of imatinib serum levels is an interesting tool that may help in cases of higher-than-expected toxicity to standard doses of imatinib in patients with response failure or sub-optimal response, on suspicion of non-adhesion to treatment and in cases which drug interactions are suspected.[9,15] Sensitive methods to determine imatinib in biological fluids are required to conduct TDM, pharmacokinetics and metabolic studies.[25]

There are several published methods to determine levels of imatinib and its main metabolite norimatinib in human plasma. The European Treatment Outcome Study (EUTOS) recommends high performance liquid chromatography (HPLC) coupled with selective tandem mass spectrometric detectors (LC-MS-MS).[24] The coupling of these two techniques combines the advantages of chromatography (high selectivity and separation efficiency) with the advantages of mass spectrometry (obtaining structural information, molecular weight and further increase in selectivity).[26] However, many authors have proposed measurement by HPLC with ultraviolet (UV) detectors, especially because of the presence of an intense chromophore at 265 nm in an acid medium.[25,27-32] LC-MS-MS is a faster, more selective and sensitive method with a greater specificity and which needs a smaller sample volume, however this equipment is more expensive as is its use.[24,25,33] Recent studies have compared HPLC with UV/diode array detection to LC-MS-MS and found no significant differences between the two methods.

The disadvantages of the HPLC-UV system compared to LC-MS-MS include the relatively long time for the analysis, lower sensitivity leading to the need of larger samples and lower selectivity as well as possible interference from endogenous compounds and other drugs which are being used concomitantly.[25] The specificity of the test can be improved by using a diode array detector (DAD), allowing spectral comparisons and peak purity control.[31,33] Thus, HPLC-DAD systems are not only sufficiently specific and sensitive for TDM of imatinib but are also more widely available instruments in laboratories and hospitals.[25,31]

Plasma exposure can be evaluated through the area under a concentration-time curve or by the obtained concentration at a certain, strictly standardized, time after medication. One of the most used time points is immediately before the administration of the next drug dose. The concentration observed at that moment is called the trough concentration as it is the lowest that the patient will experience. Therefore, it allows the sample to be dosed once and to have lower interindividual variability. The standard time proposed for the TDM of imatinib is 24 hours after dose administration in cases of a single daily dose and 12 hours after administration in the cases of two doses per day.

However, as to collect the plasma exactly at this moment may be operationally difficult. Wang et al.[23] developed a pharmacokinetic model to correct imatinib trough plasma levels obtained at different sampling times and proposed an algorithm

for TDM of imatinib in an acceptable time window for sampling. Using this algorithm allows an extension of the collection time window to 6 ± h from the standard time, i.e. between 18 h and 30 h after the last dose administration, if a single daily dose is used. Nevertheless, in order to make the algorithm reliable, the time of the last dose and last sampling time should be recorded accurately. The Schmidli et al.[34] model was used to develop the algorithm. This model is based on a large body of pharmacokinetic data from phase III of the IRIS study and estimated correction factors for variations in imatinib plasma concentrations from the standard time of the collection ± 6 h.

It is not necessary to use a correction factor in patients for whom collection is within ± 3 h from the standard sampling time. However as the time between drug administration and sampling increases or decreases by one hour above this 3 h period (up to a maximum of six hours), the concentration should be multiplied by the corresponding correction factor.

Mathematically and intuitively, the algorithm is applicable and can reduce the variability of trough pharmacokinetic evaluations, facilitating blood collection and TDM in the clinical setting. On the other hand, additional studies are still needed to validate the accuracy and the clinical benefit of this new sampling method for TDM.

Imatinib plasma levels and their clinical application

Like all oral medications, changes in the intake of imatinib (lack of adherence to treatment), absorption, metabolism, plasma protein binding, influx and efflux into the cell and enzyme inactivation may also interfere in the therapeutic action, leading to a decrease in drug plasma levels.[9] According to Larson et al.[14] patients with lower imatinib plasma levels had higher rates of discontinuation and a higher percentage of patients stopped treatment because of unsatisfactory therapeutic effect. These data suggest that patients are more likely to achieve a satisfactory level of response to therapy or an improvement in response rates if an appropriate concentration of trough imatinib is reached and maintained.

Patients with complete cytogenetic response (CCR) have higher imatinib plasma levels (IPL) than patients without CCR, a situation repeated in patients with major molecular response (MMR).[14,15] In the study performed by Larson et al.,[14] patients with CCR maintained imatinib trough plasma levels at a mean of 1009 ± 544 ng/mL, while those who did not attain CCR presented levels of 812 ± 409 ng/mL. There were no significant differences found in the responses to different doses (400 mg or 600 mg), only in relation to the IPL achieved by patients in the Picard et al.[15] study. Hence, it is important that the trough plasma level of imatinib is higher than 1002 ng/mL in order to achieve CCR.

Moreover, knowing that results of CCR and MMR can be prognostic for the effectiveness of CML treatment in the long-term in respect to protection against disease progression, TDM of imatinib plasma levels may be useful to manage patients with CML; at least it should be applied in case of treatment failure or sub-optimal response.[14,15] Recently, Takahashi et al.[35] supported these findings with a study of a cohort of 242 patients in which it was observed that trough concentrations of imatinib over 1002 ng/mL are associated with a significantly higher probability of achieving MMR (p-value = 0.0120) when compared to lower plasma levels.

The diagnosis and treatment of CML require access to the laboratory structure to perform essential examinations such as complete blood count and cytogenetic and molecular evaluations. Yet the list of desirable tests has been extended as experience in the target-specific treatment of CML increases. As for example the plasma dosage of imatinib, or even the search for clone evolution and abl mutations which should be investigated when TDM is not enough to identify treatment failure.[9,36] The evaluation of serum levels, although still not widely available in practice, can contribute greatly in the management of patients.[9]

Conclusion

The monitoring of plasma concentrations of imatinib is useful to guide therapeutic decisions, offering important guarantees for patients and health professionals, especially considering the great pharmacokinetic variability of this drug. The determination of imatinib can be adequately performed using HPLC with ultraviolet (UV) or diode array detectors (DAD), methodologies that are accessible to many laboratorial diagnosis services. Once testing is more widely available, it may become a part of the clinical management of patients on imatinib and assist in specific situations.

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