Clinical pharmacology of the tyrosine kinase inhibitors imatinib and sunitinib

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11 General Discussion and Future Perspectives

Introduction

Tyrosine kinases regulate cellular proliferation, survival, differentiation, function, and motility[1]. In the 1980s the first aberrant protein (BCR-ABL) leading to uncontrolled tyrosine kinase activity was discovered[2]. This fusion protein was the product of the minute chromosome, later known as the Philadelphia chromosome, discovered in chronic myelogenous leukemia (CML) by Nowell and Hungerford in 1960[3]. Since the discovery of BCR-ABL, several tyrosine kinases have been associated with development of cancer. For example, human epithelial growth factor (HER2) is expressed in ~25% of all breast cancers[4], BCR-ABL is expressed in ~90% of Philadelphia chromosome positive CML[5] and cKIT is expressed in ~85% of gastrointestinal stromal tumors (GIST)[6]. The tyrosine kinases are deregulated as a result of protein fusion, mutations or increased/aberrant expression of a receptor tyrosine kinase, its ligand, or both[1]. Because tyrosine kinases appear to be important in cancer biology they were interesting proteins for targeted anticancer therapy. Since 2001, eight tyrosine kinase inhibitors (TKIs) are approved for the treatment of specific malignancies. In this thesis the clinical pharmacology of two TKIs, imatinib and sunitinib, were studied and described. Imatinib is the first licensed TKI and is approved for the treatment of Philadelphia chromosome positive (Ph+) CML and for cKIT positive unresectable and/or metastatic malignant GIST[7-9]. The second drug studied, sunitinib, is approved for the treatment of GISTs after failure of imatinib therapy as well as for the treatment of advanced and/or metastatic renal cell carcinoma (mRCC)[10-12].

Pharmacokinetic aspects

TKIs appear to have very similar pharmacokinetic profiles (**chapter 2**). However many pharmacokinetic aspects remain to be studied because most of these drugs received accelerated approval before completing all intended studies, since they are used for serious life-threatening diseases with poor treatment options available. For example, imatinib was introduced onto the marked for CML after one phase I and three phase II trials[7, 13-16]. The applicant committed e.g. to provide complete follow-up safety and efficacy, to conduct a dose finding study in children, to study imatinib pharmacokinetics in patients with liver impairment and to study the influence of cytochrome P450 (CYP) 3A4 inducers on imatinib exposure after drug approval[17, 18]. Sunitinib was also approved under accelerated approval regulations for the treatment of mRCC with the commitment to provide additional information on e.g. the efficacy and safety after complete follow-up, provide additional information on the adverse effect 'left-ventricular ejection fraction', provide an analysis on the relation between exposure and efficacy outcomes and report the pharmacokinetics

of sunitinib in liver impaired patients[i]. After drug approval, case reports and investigator driven interactions and drug disposition studies are published that provide additional insight in involvement of enzymes and drug transporters important in drug disposition. For instance the influence of the adenosine-5'-triphosphate (ATP) binding-cassette (ABC) drug transporters B1 and G2 on imatinib and sunitinib disposition was discovered after approval of the drug by independent researchers[19-21]. The clinical relevance of the affinity and inhibition capacity of sunitinib and imatinib for these transporters needs to be further addressed in additional research.

The clinical relevance of the principal metabolic pathways is typically investigated in healthy volunteers after a single dose of the drug of interest in pharmacological studies before drug approval. However, the clinical relevance of these apparently important enzymes at steady-state pharmacokinetics is usually unknown. In **chapter 3** an absent effect of ritonavir, a potent CYP3A4 inhibitor, was observed on steady-state imatinib pharmacokinetics while CYP3A4 is claimed to be the dominant metabolic route of imatinib. For imatinib some extra studies have been dedicated to the effect of the less dominant enzymes[22-24]. CYP1A2 is one of these minor enzymes in imatinib metabolism. However an absent effect of CYP1A2 induction, by cigarette smoking, on imatinib pharmacokinetics was observed in the study described in **chapter 4**. Still many metabolic pathways in imatinib metabolism need to be explored and additional research is required to better define important enzymes at steady-state imatinib pharmacokinetics in cancer patients. Additionally, the uptake of imatinib from the rectum was measured and described in **chapter 5**. It appears that imatinib is moderately absorbed from the rectum and this route of administration could be considered when oral intake is impossible.

Only little information on the metabolism of sunitinib is available[25, 26]. Since the TKIs appear to have a very similar pharmacokinetics profile many pathways known for other TKIs could be of interest for sunitinib. Additionally, the effect of sunitinib on drug disposition of co-administered drugs has not been investigated in cancer patients at steady-state pharmacokinetics. Therefore, the effect of sunitinib on midazolam exposure and the effect of grapefruit juice on sunitinib exposure have been studied at steady-state sunitinib pharmacokinetics in cancer patients. Sunitinib appears to have an inducing effect on CYP3A4 activity (**chapter 6**) which needs confirmation. Coincidently, a very potent inducing effect on CYP3A4 by mitotane was observed, resulting in decreased sunitinib and midazolam exposure (**chapter 9**). Grapefruit juice increases the relative bioavailability of sunitinib to a clinically non-relevant extent (**chapter 8**), and therefore no scientific evidence was found for the warning in the sunitinib label regarding grapefruit juice consumption.

i Pfizer Inc., Sutent (sunitinib malate): Letter action date 01/26/2006 [accessed 2009 February 24]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Interpatient variability in drug exposure

The interpatient variability in drug exposure is large, ~40% for both imatinib and sunitinib, similar to the reported variability of all TKIs[18, 26-29]. The study of van Glabbeke et al. demonstrated that imatinib related toxicities are highly dose dependent and thus associated with imatinib exposure[30]. On the other hand, lower trough levels of imatinib appeared to be associated with a decreased efficacy to imatinib therapy[31, 32]. Although little data is available on the relation between sunitinib exposure and toxicity or efficacy, a similar relationship is hypothesized. Sunitinib dose escalation results in a proportional increase in sunitinib trough levels. At increasing dose levels more dose limiting toxicities were observed[33]. An association between sunitinib trough levels and treatment response has not been published yet. The large interpatient variability can result in either unintended toxicity response as well as in decreased therapeutic response. Hence identification of factors affecting the pharmacokinetic profile of TKIs could aid in predicting and adjusting the individual doses to prevent toxic response or therapeutic failure[22]. In the population pharmacokinetic approach of Widmer et al. multiple variables that might explain for the large interpatient variability of imatinib such as age, body weight, gender, disease and α-1 acid glycoprotein were explored. Only α-1 acid glycoprotein explained a substantial part of the interpatient pharmacokinetic variability[28]. For sunitinib, only recently, a study has been described in which variables were explored that could explain for the large interpatient variability in pharmacokinetics. Body weight, gender, race, elevated ECOG performance status, and tumor type explained a substantial part of the interpatient variability in the apparent clearance; body weight and gender explained a part of the interpatient variability in the volume of distribution. However, the major part of the interpatient variability in sunitinib pharmacokinetics remains unexplained[34]. Besides the patient characteristics and the physiological parameters, also the activity of both the enzymes and transporters might be of great influence on the large interpatient variability. Both imatinib and sunitinib are substrates of ABCB1 and ABCG2[19, 21]. The genes encoding these transporters are highly polymorphic which could significantly influence drug absorption[35]. Additionally, functional polymorphisms in enzymes can decrease or increase the metabolic capacity. Genotyping as well as phenotyping of enzymes and transporters might help us to explain a large part of the interpatient variability. Several studies have investigated the effect of transporter polymorphisms on imatinib exposure. *ABCB1 1236T>A*, *ABCB1 2677T>A* and *ABCG2 421C>A* polymorphisms appear to effect imatinib trough levels[36-38]. Similarly the CYP2D6*4 polymorphism results in an increase in imatinib exposure[22]. For sunitinib no studies are available associating genetic polymorphisms in transporters or enzymes and drug exposure. However, an effect of polymorphisms in enzymes and transporters is hypothesized since sunitinib is also a substrate for CYP3A4, ABCB1 and ABCG2 and exploring such associations seems interesting to investigate. In **chapter 7** the relation between sunitinib-induced toxicity and polymorphisms in genes encoding

metabolizing enzymes, drug transporters, targets are described. Polymorphisms in the genes *CYP1A1*, *ABCB1*, *ABCG2*, *NR1I3*, *VEGFR-2* and *FLT3* appear to be associated with the development of sunitinib-induced toxicity. Both imatinib and sunitinib are extensively metabolized by CYP3A4[18, 26]. CYP3A4 is also highly polymorphic; however clinically significant polymorphisms are very uncommon and therefore only a limited role for CYP3A4 pharmacogenetics is predicted[39]. A CYP3A4 phenotypic approach to predict the systemic exposure to imatinib and sunitinib might instead very well explain the large interpatient variability in pharmacokinetics[40]. In **chapter 6** the relation between CYP3A4 activity, determined by midazolam exposure, and sunitinib were investigated and a good relation between the activity of CYP3A4 and sunitinib exposure as well as with sunitinib trough levels was found.

Mechanisms of resistance

Resistance to imatinib and sunitinib therapy can be subdivided into two separate mechanisms: tyrosine kinase reactivation in the presence of a TKI by for example gene amplification or point mutations or the development of resistance which is independent of the tyrosine kinase activity[41].

Point mutations in the tyrosine kinase are the most common reason for the development of TKI resistance. Indeed, for imatinib resistance, various secondary mutations in BCR-ABL have been characterized. Mutations in the adenosine triphosphate (ATP) binding loop (P-loop) of BCR-ABL are frequently observed and associated with a poor response[42]. Most GISTs harbor (primary) mutant c-KIT (~80%) or platelet-derived growth factor receptor α (~5-7%). ~14% of the GISTs exhibit primary resistance to imatinib, additionally another 40-50% develop resistance within 2 years of therapy[43]. GIST responsiveness to imatinib varies for the different primary *c-KIT* genotype; exon 11- mutant GISTs are more sensitive than exon 9-mutant or wild-type GISTs. In contrast, progression free and overall survival on sunitinib therapy were significantly longer for primary *c-KIT* exon 9 mutations and the wild type genotype compared to exon 11 mutations. Secondary point mutations are common in GISTs that show secondary resistance but not in those that exhibit primary resistance. Secondary point mutations are usually located in the drug/ATP binding pocket of the receptor (exon 13 and 14) or in the activation loop (exon 17). In patients that exhibit resistance to imatinib because of secondary point mutations the progression free and overall survival for sunitinib were longer for patients who had secondary *c-KIT* exon 13 or 14 mutations than those with secondary *c-KIT* exon 17 or 18 mutations. Secondary mutations in the activation loop (exon 17 and 18) are insensitive to imatinib and sunitinib therapy[43]. Associations between primary and secondary mutations in tyrosine kinases, important in renal cell carcinoma, and response to sunitinib therapy have not been discovered yet.

Besides the specific tyrosine kinase related resistance, it is thought that exposure levels (pharmacokinetics) also may play a role in the initial or secondary resistance. Recently, a correlation was observed between clinical effect in CML (defined as major molecular response and complete cytogenetic response) and a minimal trough level of imatinib, indicating that inadequate drug exposure levels could also result in initial or secondary imatinib resistance[31]. A minimal exposure to imatinib and sunitinib is also suggested for the effective treatment of GIST and mRCC, although studies supporting this hypothesis have not been performed yet. Several possible mechanisms have been described resulting in an inadequate drug exposure; i) increased levels of the acute phase binding protein (α acid glycoprotein (AAG)) resulting in a reduced free fraction of the drug[28, 44], ii) increased functionality of the highly polymorphic efflux transporters ABCB1 and ABCG2[21, 35-37], iii) upregulated drug clearance by increased activity of metabolizing enzymes[22, 40]. Additionally, the exposure to the drug can decrease over time due to increased drug clearance[27].

Future research perspectives

In the recent years important progress has been made in unraveling the pathophysiology of cancer. With this gaining insight, targeted therapies, that can specifically inhibit deregulated cellular processes important for maintenance of the malignancies, have been and are being developed. Ultimately, this may lead to an approach of cancer as being a chronic disease instead of a life threatening disease. A major challenge to address in the treatment of chronic cancerous disease is how to circumvent antitumor drug resistance.

With the better characterization of tumor biology and the somatic mutations resulting in tumor progression, the disease could be treated on a more individualized and targeted basis. For example, GIST tumors harboring specific mutations in the cKIT receptor that respond better to either imatinib or sunitinib might better be treated based upon somatic tumor characteristics rather that the first line, "one size fits all" approach. Drug development of anticancer drugs for tumor subtypes harboring specific somatic mutations rather than for anatomic or histological tumor subtypes may lead to more effective therapies and less tumor resistance. However, this approach may be in conflict with the study design of pharmaceutical industry at this moment in which antitumor drugs are developed for large groups of patients and it is therefore questionable whether we can expect this somatic mutation driven approach from industry studies. For GIST tumors the role of *cKIT* mutations for imatinib and sunitinib sensitivity are thoroughly investigated and better understood. However, for mRCC and many other tumors these investigations for tumor subtype specific drug sensitivity should be performed in the nearby future.

Additionally, genotypic features in drug targets, enzymes and transporters might predispose

for development of side effects to antitumor therapy. The drug targets are not solely expressed on tumor tissues but also on "healthy" cells responsible for physiological processes in our body. Affinity differences, due to genetic alteration, of the drug for the targets could result in a more or less pronounced effect on normal cells and thereby results in toxicity. By better characterization of factors that result in toxicity, therapies can be selected that have a favorable toxicity profile which will result in a better adherence to and acceptance of the therapy and less required dose adjustments. Dose adjustments due to toxicity could be harmful since subtherapeutic exposure levels for an adequate antitumor response might be generated. Also polymorphisms in genes encoding enzymes and transporters important for drug metabolism and disposition can lead to toxicity or inefficacy as a result of higher or lower exposure levels.

Enzymes and transporters claimed to be important at time of drug approval are typically identified in *in vitro* studies and confirmed in single dose interaction studies in healthy volunteers. The warnings for co-administered drugs and food in the drug label are based upon extrapolations from these single dose interactions studies. Since TKIs are administered on a daily basis and some appear to be substrates as well as inhibitors of their own metabolic and disposition pathway, the enzymes and transporters that are important at steady-state pharmacokinetics in cancer patients could be very different from those identified just after starting therapy as we have demonstrated in several studies described in this thesis. Therefore, pharmacological studies at steady-state pharmacokinetics using phenotypic probes should be done to identify the enzymes and transporters that are important in drug metabolism and disposition. This will result in better scientifically based warnings in the drug label for drugs and food that should not be co-administered. This may ultimately result in more reliable medication surveillance by physicians and pharmacists resulting in less sub- and supratherapeutic exposure levels in patients treated with these drugs.

For all TKIs, except for imatinib in CML treatment, minimal exposure levels or minimal trough levels required for a therapeutic response are unknown. A complicating factor is that different tumors (depending on different TKs) and tumor subtypes (with different somatic mutations) will require different concentration levels due to sensitivity differences. Inadequate drug concentrations could result in either tumor progression or drug related toxicities. I would like to hypothesize that subtherapeutic concentrations results in the selection of less sensitive cells which, by generating secondary mutations, results in drug resistance. Based on data from dose limiting toxicity studies (phase I trails), initially a fixed dose is used for the treatment with TKIs, regardless of the sensitivity of the tumor or the individual drug concentration. Only during phase I studies pharmacokinetics data are collected while the therapeutic response is monitored during phase II and III trails. A better determination of the relation between drug concentrations and disease response during phase II and III trials could help us in individualizing treatment aimed at preventing therapeutic failure and toxicities. The TKIs are generally administered in a daily regimen and thereby suppress tumor growth continuously. Interesting parallels between the therapy with TKIs and antiretroviral therapy (used in HIV infections) which also encounters resistance can be drawn. The interindividual variability is large for all TKIs and determinants for this large variability are at least partly unknown. The "fixed dose for all tumors approach" that is applied will not result in the aimed exposure level or the aimed trough level in all patients due to the large interpatient variability. Therefore therapeutic drug monitoring (TDM) could become important in the treatment of cancer for this group of drugs. Initially, it needs to be established which PK parameter associates best with therapeutic response. Limiting sampling makes TDM more feasible. Therefore after establishing the most suitable PK parameter effort should be invested in determining the minimal amount of samples needed to obtain the parameter. For sunitinib for example we have investigated that trough levels correspond well with exposure levels, which makes trough level monitoring suitable for both concentration threshold as well as exposure determination. The monitoring just after starting therapy is required to adjust the dose until the aimed drug concentration is reached. However, since the drug concentration can decrease over time, repeatedly monitoring would be required. For most TKIs the correct PK parameter that relates to therapeutic response needs to be identified and additionally a limiting sampling approach needs to be defined.

Although a promising group of new drugs have been discovered and are used in the treatment of malignancies still great profit can be achieved by a better understanding of important pharmacogenetic and pharmacokinetic features of these drugs which could result in a more individualized approach with less toxicity and more efficacy.

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