Clinical pharmacology of the tyrosine kinase inhibitors imatinib and sunitinib

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Summary

Every year approximately 3.2 million Europeans are diagnosed with cancer and with ~1.7 million deaths from cancer per year it is the second most common cause of death[i]. In the Netherlands approximately 83 thousand persons are diagnosed with cancer each year and the mortality incidence is around 40 thousand persons a year[ii]. Although, multiple anticancer therapies have been developed in the recent years, the quest for novel therapies which harbors better efficacy and less toxicity is still an important topic.

In the 1980s a group of possibly interesting proteins, tyrosine kinases, in cancer biology were discovered. Tyrosine kinases (TKs) are enzymes that catalyze the transfer of phosphate from adenosine triphosphate (ATP) to other cellular proteins and thereby regulate several crucial processes regarding survival, proliferation and motility of cells. The activity of TKs is normally under tight control. However, in multiple cancers TKs appear to be deregulated which make them interesting targets for anticancer therapy. In 2001 the first tyrosine kinase inhibitor (TKI), imatinib, was registered for the treatment of BCR-Abl positive chronic myelogenous leukemia (CML). Since the introduction of imatinib, seven other TKIs have been registered and more TKIs will be introduced in the near future. Although these TKIs were initially introduced as the "magic bullets" that would be highly tumor-cell specific and thus highly antitumor effective with only minor toxicity towards normal cells, limitations were soon encountered. The development of resistance and the occasionally observed toxicities constitute the major challenge in the treatment with TKIs.

A better understanding of the pharmacokinetics of TKIs might help us to prevent sub- or supratherapeutic exposure to these drugs. Additionally, a better understanding of polymorphisms in the pharmacokinetic and pharmacodynamics pathways of the TKIs might also help us to prevent toxicities and to optimize tumor response by individualizing the dose and choice of antitumor therapy. This thesis focuses on the pharmacokinetics of imatinib and sunitinib in cancer patients and on the use of different tools, phenotyping and pharmacogenotyping, to optimize and individualize TKI therapy.

TKIs represent a relatively new and fast growing group of anticancer drugs developed as oral formulations which are administered in cancer patients in a daily regimen. Most of the current knowledge of the pharmacokinetic behavior of the TKIs is derived from *in vitro* experiments, animal studies, drug-drug interaction studies and mass balance studies in healthy volunteers with a single dose of the aimed TKI. However, since this group of drugs is administered in a daily schedule, other enzymes and drug transporters might become important at steady-state pharmacokinetics, which could result in adjusted warnings for co-administered drugs and food. In **chapter 2** an overview is provided of the current knowledge on the

i   http://ec.europa.eu/health
ii   http://www.ikcnet.nl

pharmacokinetic aspects; absorption, distribution, metabolism, excretion (ADME), drug transporters and drug-drug interactions of the eight registered TKIs: imatinib, gefitinib, erlotinib, sorafenib, sunitinib, dasatinib, lapatinib and nilotinib. Additionally, the similarities and differences between these apparently related TKIs are summarized.

Clinical pharmacology of imatinib

Imatinib is predominantly metabolized by the enzyme cytochrome P450 3A4 (CYP3A4) and is therefore prone to drug interactions with co-administered drugs, food, and herbal supplements. The warnings for CYP3A4 inducers or inhibitors are based on drug interaction studies with a single-dose of imatinib. However, it is unknown if similar drug interactions occur at steady-state imatinib pharmacokinetics. Therefore, the effect of ritonavir, a potent CYP3A4 inhibitor, on steady-state imatinib in cancer patients was investigated (**chapter 3**). Surprisingly, imatinib appears to be insensitive to potent CYP3A4 inhibition by ritonavir at steady-state. Since imatinib is a CYP3A4 inhibitor itself it is hypothesized that the drug relies on alternate elimination pathways after prolonged exposure due to autoinhibition of CYP3A4. For drugs with complex elimination pathways, such as imatinib, interaction studies that are performed after a single dose may not provide us with correct information applicable for clinical practice. Therefore, it is preferred to perform interaction studies at steady state pharmacokinetics which better represents the clinical situation since other enzymes, that only play a secondary role in *in vitro* experiments, could play a dominant role at steady-state.

Possible interesting cytochrome enzymes for imatinib metabolism are: CYP1A1, CYP1A2, CYP2C9, CYP2C19, and CYP2D6. CYP1A2 is induced by cigarette smoking and therefore smokers might be exposed to lower blood concentrations of imatinib than non smokers. In **chapter 4** the effect of smoking on imatinib pharmacokinetics, safety, and efficacy was investigated. The results of this study did not reveal a dominant role for CYP1A2 in imatinib metabolism since smoking did not alter the pharmacokinetics and thereby the exposure to imatinib. Interestingly, smoking was related to an increased risk for grade ≥2 anemia and fatigue and additionally showed a shorter overall survival and a shorter time to progression on treatment with imatinib. However, these last two observations warrants further confirmation.

Coincidently, one of the patients who volunteered in the imatinib pharmacokinetic study was admitted to the hospital a year later with tumor-related intra-abdominal obstructions and diffuse intra-abdominal bleedings. Due to gastro-intestinal obstruction the patient was unable to take the imatinib tablets orally; therefore the tablets were administered rectally. The uptake of imatinib after rectal administration is described in **chapter 5**. The imatinib

exposure after rectal administration appeared to be approximately 40% of the exposure reached after oral administration. Therefore, rectal administration could be considered in situations were oral intake of the tablets is impossible.

Clinical pharmacology of sunitinib

Sunitinib is a multitargeted tyrosine kinase inhibitor, known to inhibit vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3, platelet-derived growth factor receptor (PDGFR) α and β, KIT, Fms-like tyrosine kinase 3 receptor (FLT3), and the receptor encoded by the ret proto-oncogene (RET). The drug is approved for the first line treatment of metastatic renal cell carcinoma (mRCC) and imatinib resistant metastatic GIST. The toxicity profile of sunitinib is pronounced and includes e.g.: fatigue, mucosal inflammation, cardiotoxicity and myelo-suppression. Approximately 30% of the patients treated with sunitinib need a dose reduction or interruption due to adverse events making toxicity a limiting factor in the successful treatment with this drug. In the following chapters several approaches have been explored with the aim to individualize sunitinib therapy and thereby reduce toxicity. Additionally, the effect of CYP3A4 inhibition on sunitinib exposure as well as the effect of sunitinib on CYP3A4 activity is studied in drug-interaction studies.

In **chapter 6** the possible use of the noninvasive CYP3A4 phenotypic probe, midazolam, to predict sunitinib exposure was explored. Additionally the relation between sunitinib plasma trough levels and sunitinib exposure was determined since monitoring sunitinib trough levels provide a more feasible and assessable approach to study exposure-effect and -toxicity relations. Moreover, the effect of sunitinib on CYP3A4 activity was evaluated. Since sunitinib is solely metabolized by CYP3A4, the activity of CYP3A4 might explain the large and yet unexplained interpatient variability (~40%) in sunitinib clearance. The activity of CYP3A4 can be determined by the phenotypic probe midazolam which is also mainly metabolized by CYP3A4 without exerting influence on the activity of this enzyme. It appears that midazolam exposure relates well to sunitinib exposure as well as sunitinib trough levels and explains a large part of the interpatient variability in sunitinib clearance. Also a strong relation was found between sunitinib trough levels and sunitinib exposure which legitimates the use of sunitinib trough levels instead of the multiple sampling approaches to determine exposure-effect and –toxicity relationships. Additionally, sunitinib appears to be a mild CYP3A4 inducer however this observation needs confirmation.

Both genes encoding the sunitinib targets (VEGFR1, -2 and -3, PDGFR-α and PDGFR-β, KIT, FLT3, and RET), as well as genes encoding the enzymes and efflux transporters involved in sunitinib's disposition and metabolism are highly polymorphic and may be related to the differential toxicity response in patients treated with sunitinib. The identification of genetic

markers related to toxicity outcomes in the pharmacokinetic and pharmacodynamic pathways of sunitinib are described in **chapter 7**. The selected toxicity outcomes; thrombocytopenia, leucopenia, mucosal inflammation, hand-foot syndrome and any toxicity > grade 2, were based on the results of a published placebo controlled study. We selected toxicities that appear to be causally related to sunitinib treatment. Thrombocytopenia was not associated with any of the genetic polymorphisms studied. Polymorphisms in *FLT3, NR1I3 and CYP1A1* were related to leucopenia. The same polymorphism in *CYP1A1* was related to mucosal inflammation. Hand-foot syndrome appeared to be related to a polymorphism in *ABCB1*. Finally any toxicity > grade 2 was associated with polymorphisms in *VEGFR2* and *ABCG2*. The polymorphisms identified in this study should be regarded as hypothesis generating and need to be confirmed in an independent group of patients.

Since CYP3A4 appears to be the most important enzyme in the metabolism of sunitinib the drug label warns for multiple drugs and food substrates known to interfere with the activity of this enzyme. However, most of these warnings are not based on study results but rather are extrapolations of the observed interaction with model drugs such as rifampicin (CYP3A4 inducer) and ketoconazol (CYP3A4 inhibitor). Grapefruit juice is a potent CYP3A4 inhibitor of the enzymes located in the intestines. The effect of grapefruit juice on the bioavailability of sunitinib has not been studied yet. Nevertheless, the drug label of sunitinib advises patients to avoid the consumption of this juice. In **chapter 8** the effect of grapefruit juice on steady-state sunitinib exposure was evaluated. The co-administration of grapefruit juice with sunitinib resulted in an 11% elevation of sunitinib bioavailability which is not regarded as clinically relevant.

Two patients in the sunitinib pharmacokinetic study described in chapter 8 showed aberrant pharmacokinetics of sunitinib and midazolam, the latter being used as a CYP3A4 phenotypic probe (**chapter 9**). Both patients were also treated with mitotane which appeared to be a very potent CYP3A4 inhibitor.

As described before, grapefruit juice is a potent inhibitor of intestinal CYP3A4 enzymes. However it has no effect on the same CYP3A4 enzymes located in the liver. An explanation for this unexpected effect is not found yet. A possible explanation could be that the active ingredients in grapefruit juice are not absorbed across the intestinal wall.

Chapter 10 describes the absorption of two active ingredients in grapefruit juice in healthy volunteers after consuming large quantities of the juice: bergamottin (BG) and 6',7'-dihydroxybergamottin (DHB), which are held responsible for CYP3A4 inhibition. Additionally the amount of BG and DHB in different brands and lots of grapefruit juice was quantified. The two ingredients, BG and DHB, were undetectable both after single and multiple consumptions of grapefruit juice. Therefore, the lack of substantial absorption of BG and DHB probably explains why grapefruit juice has an inhibitory effect on intestinal CYP3A4 only and not on hepatic CYP3A4. The large variability in concentration BG and DHB between different brands and lots of grapefruit juice necessitates quantification of these ingredients in order to make the interpretation of the results and comparison between different interaction studies possible.

In the final **chapter** the results of this thesis are discussed and possible future directions are outlined. Future developed antitumor treatments will more specifically interact with the underlying mechanism responsible for deregulation of cellular growth control in tumor cells. With a better understanding of tumor biology, a more individualized approach will probably be reached resulting in the application of targeted drugs developed to inhibit specific tumor subtypes. Individualization will also result in the selection of the right individual patients that profit most an endurable toxicity profile. Additionally, monitoring the exposure to the drugs and adjusting the individual dose based on the exposure level measured will contribute to the optimization of antitumor response and limitation of drug related toxicities. Much effort will be needed to determine the exposure-effect and exposure-toxicity relation for the different tumor subtypes and patients. The use of predictive biomarkers and therapeutic drug monitoring will probably become more important in future antitumor treatment.