Chapter 1

General introduction
Cancer is the second leading cause of death worldwide, after cardiovascular disease, accounting for 79 million deaths; ~ 13% of all deaths in 2007. Additionally the incidence of cancer is increasing. The five most mortal types of cancer are; lung, stomach, liver, colorectal and esophageal cancer. Over 30% of cancer can be prevented by not using tobacco, having a healthy diet, being physically active and by preventing infections that may cause cancer. Once diagnosed, there are several different types of treatment ranging from resection (surgery), to radiation (radiotherapy), to systemic therapy used as adjuvant or palliative therapy. The conventional cytotoxic chemotherapeutic agents have a generic working profile that interact non-specifically with cellular DNA and/ or tubulin resulting in growth arrest of all fast growing cells. With the increased understanding of cancer biology, rational design of targeted drugs has started. Targeted drugs have antitumor activity in selected subgroups of tumors expressing proteins that are specific for the malignant phenotype. The clinical use of targeted therapy started with the development of monoclonal antibodies. Five years later, the first tyrosine kinase inhibitor was approved for cancer treatment. Tyrosine kinase inhibitors are a class of targeted therapy that is designed to compete with adenosine-5'-triphosphate (ATP) for the ATP-binding pocket within the intracellular domain of wild type and/or mutated tyrosine kinase receptor and thereby blocks downstream signaling important for tumor growth. Imatinib is the first rationally designed tyrosine kinase inhibitor approved in 2001 for the treatment of three Philadelphia chromosome positive leukemia subtypes. Since 2001, seven additional tyrosine kinase inhibitors have been approved, all rationally designed to be active against specific tyrosine kinases. These targeted drugs tend to have a better toxicity profile than traditional cytotoxic chemotherapy that interacts non-specifically resulting in more collateral, transient damage in healthy tissues. With the introduction of tyrosine kinase inhibitors a new era of treating tumors has started.

All tyrosine kinase inhibitors exhibit rather similar pharmacokinetic characteristics. They are all highly protein bound, have a long half life and a large volume of distribution, they are all primarily metabolized by cytochrome P450 (CYP) 3A, and predominantly excreted with the feces. However, several pharmacokinetic aspects of these drugs are also unknown. For example, the absolute bioavailability for most tyrosine kinase inhibitors is unknown as is the clinical relevance of their interactions with (substrates for and/or inhibitors of) drug transporters on intestinal cells, hepatocytes, cancer cells and renal cells. Since these drugs are both substrates and inhibitors of their own metabolic pathways, the metabolism of these drugs at steady-state exposure is complex and unpredictable.

Therefore, the aim of this thesis is to further explore clinical pharmacological aspects of two tyrosine kinase inhibitors, imatinib and sunitinib, to better understand steady-state pharmacokinetics, clinical relevant interactions and genetic determinants that may predispose for specific side effects of these drugs.
Most information of the pharmacokinetic behavior of the tyrosine kinase inhibitors originates from preclinical studies. In addition, clinical studies have revealed important pharmacokinetic data of these drugs. An overview of the current knowledge on absorption, distribution, metabolism, elimination, drug transporter affinity and drug-drug interactions of all approved tyrosine kinase inhibitors as well as their similarities and differences will be presented in chapter 2.

Little information is available on the relevance of drug interactions at steady-state pharmacokinetics. According to the drug label of imatinib, CYP3A4 is the most important enzyme responsible for the metabolism. Since many clinically used drugs are known to inhibit or induce CYP3A4, imatinib is prone for drug-drug interactions. In chapter 3 we will determine the effect of ritonavir, a potent CYP3A4 inhibitor, on the steady-state imatinib exposure (AUC). Multiple CYP enzymes, such as CYP3A4, 3A5, 2D6, 2C9, 2C19, 1A2, 1A1, are capable of metabolizing imatinib in in vitro experiments; however there are no data available on the influence of these minor enzymes on imatinib exposure. Since we know that smoking has a pronounced effect on CYP mediated metabolism and hereby on erlotinib exposure a similar effect is hypothesized for imatinib. In chapter 4, the effect cigarette smoking on imatinib exposure will be studied.

The exact absorption-site of imatinib in the intestines is unknown. Some patients with gastrointestinal stromal tumor (GIST) may not be able to take imatinib orally, due to tumor related gastrointestinal obstruction. Therefore, in chapter 5 we will study imatinib pharmacokinetics in a patient after using the rectal route of administration.

Sunitinib, like all tyrosine kinase inhibitors, shows large interpatient variability in drug exposure which might affect the clinical outcome with respect to both toxicity and efficacy. In clinical practice – 33% of the patients need a dose interruption or a dose reduction due to drug related toxicities^{17-19}. We will explore the use of a noninvasive and harmless phenotypic probe (midazolam) to determine CYP3A4 activity and thereby predict the exposure to sunitinib before starting sunitinib therapy. The results of this study will be described in chapter 6. Most interaction studies are performed with a single dose of the drug of interest, whereas the metabolism at steady-state can be distinctly different due to auto-inhibition of the primary metabolic pathway. Some tyrosine kinase inhibitors (imatinib, dasatinib and nilotinib) appear to be both substrates and inhibitors of CYP3A4. The effect of steady-state sunitinib exposure on CYP3A4 activity is also described in chapter 6. Additionally, we will study the association between genetic variants in genes encoding enzymes, transporters and sunitinib targets and sunitinib induced toxicities (chapter 7).

Since the absolute bioavailability of sunitinib is unknown, the influence of intestinal CYP3A4 activity on sunitinib exposure is unpredictable. However, in the drug label of sunitinib there is a warning for co-administration of CYP3A4 inhibitors, such as ketoconazole, clarithromycin and indinavir, but also for grapefruit juice which is a potent inhibitor of intestinal CYP3A4.
References