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Cancer is a leading cause of morbidity and mortality [1,2]. In 2012, there were worldwide approximately 14 million patients diagnosed with cancer and 8.2 million cancer related deaths [1,2]. Considering the Netherlands, there were more than 100,000 patients diagnosed with cancer in 2014. In addition, over 42,000 patients died of cancer in that year, making it the leading cause of mortality in the Netherlands [3,4]. Once diagnosed, there are three types of treatment modalities including surgery, radiotherapy and systemic therapy which can be used both in a (neo)adjuvant and palliative setting.

In the last two decades, the systemic treatment options with anticancer drugs in oncology have changed remarkably. With the increased understanding of cancer pathophysiology, the treatment of several cancers has shifted from the use of nonspecific chemotherapy aimed at killing all dividing cells, towards more specific treatment with (oral) targeted therapies and immunotherapy. Targeted drugs inhibit the growth of cancer by interfering with specific target molecules involved in the growth, activation and differentiation of cancer cells and therefore act more specific when compared to conventional therapies.

Tyrosine kinases are such specific molecules and these proteins have become an important target for anticancer drug design. Tyrosine kinases transfer phosphate from adenosine-5’-triphosphate (ATP) to tyrosine residues on cellular proteins which activates signal-transduction pathways [5]. Insights into the dysregulation of these pathways in cancer cells led to the development of tyrosine kinase inhibitors (TKIs). TKIs compete with ATP for the ATP-binding pocket of tyrosine kinases that are mutated or overexpressed in some cancer cells and hereby block the dysregulated signal-transduction pathways critical for the growth, activation, differentiation and death of (cancer) cells [5]. With the introduction of the first TKI imatinib in 2001, a whole new era of rationally designed TKIs has emerged. Since then, 22 other TKIs have been registered by the European Medicines Agency for the treatment of different types of both solid as well as hematological cancers [6].

Another important target for anticancer drug design is the mammalian target of rapamycin (mTOR), a serine-threonine kinase that is a key signaling molecule in the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [7]. This pathway is involved in the regulation of growth, proliferation, metabolism, survival and angiogenesis of cells and dysregulated in cancer. Everolimus and temsirolimus are examples of oral targeted therapies that specifically inhibit mTOR and that are used in oncology.

In recent years, the clinical pharmacology of oral targeted therapies including TKIs and everolimus has been studied extensively [8-10]. Despite the large variability in pharmacokinetics (PK) between patients, all TKIs, as well as everolimus, are registered at a fixed oral dose. This results in large differences in exposure between patients. As evidence for a relationship between drug exposure and treatment outcome is growing for TKIs, fixed dosing could potentially result in sub- or supratherapeutic drug exposure with decreased therapeutic effects in some patients or an increased incidence and severity of toxicity in others [11-13]. It can be hypothesized that dose individualization could improve clinical outcomes. Interestingly, within transplantation medicine dose individualization of everolimus is already the standard of care [14]. However, in the field of oncology dose individualization of everolimus is largely unexplored.

A better understanding of the underlying causes of inter-patient variability in drug exposure of oral targeted therapies is warranted. Also, strategies should be developed to easily monitor treatment with these drugs in clinical practice. Moreover, studies that investigate the feasibility of dose individualization strategies such as therapeutic drug monitoring (TDM) are needed. Therefore, the aim of this thesis is to investigate and develop dose optimization strategies of oral targeted therapies used in oncology, in particular for the TKIs pazopanib and sunitinib and the mTOR inhibitor everolimus.

In chapter 2 a systematic overview is given of current knowledge and evidence for individualized dosing of TKIs that are used for the treatment of solid tumors. Different criteria should be met to make dose individualization for a drug of potential interest. This chapter evaluates whether TKIs meet these criteria, with an emphasis on the primary requirement; a proven drug exposure-response relationship.
A technical prerequisite for dose individualization of a drug, is the availability of a quantitative bio-analytical assay to measure drug levels and to monitor therapy in clinical practice. In chapter 3 the development and validation of a liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) assay to simultaneously detect six TKIs including pazopanib and sunitinib and two active metabolites in human serum is described.

Monitoring of drug levels in serum or plasma as described in this assay makes blood sampling by venupuncture necessary. This has several disadvantages, including its invasive character, the requirement for patients to come to the clinic and the need for trained personnel. In chapter 4 we investigate the feasibility of dried blood spot (DBS) sampling as a simple, flexible and more patient friendly alternative for the monitoring of pazopanib therapy.

In chapter 5 we describe the feasibility of TDM to optimize the dosing of pazopanib. With the use of TDM, dosing can be individualized after steady-state PK has been reached.

Another approach for dose individualization could be the use of a noninvasive phenotyping probe. With this probe, drug exposure is predicted before initiation of therapy. In chapter 6 midazolam is evaluated as a potential phenotyping probe for CYPIA4 activity to predict sunitinib exposure in patients with cancer.

Patients with gastrointestinal stromal tumours (GIST) often have an altered anatomy of the gastrointestinal tract due to either resection of the primary tumor or subsequent surgery for recurrence and/or metastasis. This could influence drug absorption and thus lead to differences in drug exposure between patients. In chapter 7 the effect of different gastrointestinal resections on sunitinib exposure in patients with GIST is investigated.

Everolimus is a promising drug for the treatment of different solid tumors such as breast cancer and metastatic renal cell carcinoma. However, many patients are in need of dose interruptions, reductions and treatment discontinuation due to toxicity of this drug. In contrast to transplantation medicine where everolimus’ dosing is based on TDM, a fixed oral and high dose of 10 mg is used in oncology. In chapter 8 the correlation between everolimus exposure and toxicity and its population pharmacokinetics in patients with thyroid cancer is evaluated.

This thesis ends with the general discussion and future perspectives in chapter 9.