9
General discussion & future perspectives

Introduction

More and more progress is being made in the unraveling of cancer pathophysiology. With this increased understanding, a whole new era of rationally designed oral targeted therapies has been developed over the last one and a half decade. Both tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors block the growth of cancer by interfering with specific target molecules involved in the growth, activation and differentiation of cancer cells. Therefore, they act more specific when compared to conventional therapies.

It is important to continue the development of innovative targeted therapies for the treatment of cancer. However, we should also try to optimize the treatment options that are currently available. Especially, since not all patients have the same beneficial treatment outcomes in term of efficacy when given the same therapy. Moreover, it was expected that (oral) targeted therapies would be less toxic than conventional chemotherapy due to their selective mode of action. However, still a significant number of patients experience, sometimes severe, adverse events leading to dose interruption and -reductions and even non-compliance or treatment discontinuation.

For many TKIs as well as everolimus, correlations between drug exposure and treatment outcome have been described, and the evidence for such relationships is gradually growing. This, in combination with their fixed dosing and reported high inter-patient variability in pharmacokinetics, has raised the hypothesis that dose optimization of these drugs may lead to better treatment outcomes both in terms of more efficacy and less toxicity.

The aim of this thesis was to investigate and develop dose optimization strategies of targeted therapies used in oncology, in particular for the TKIs pazopanib and sunitinib and the mTOR inhibitor everolimus.

Measurement of drug exposure

One of the goals of this thesis was to develop strategies to easily measure drug exposure. Both for the purposes of clinical research and for clinical practice, accurate and specific bioanalytical methods are necessary in order to retrieve reliable and comparable results. In the literature, different assays including liquid chromatography-tandem mass spectrometric (LC-MS/MS) and high pressure liquid chromatography -ultraviolet (HPLC-UV) assays have been described for the single quantification of most TKIs as well as everolimus [1-14]. However, for clinical practice it is more efficient to have a bioanalytical method that can quantify various TKIs within one run. We have successfully developed a sensitive LC-MS/MS method for the simultaneous determination of six TKIs (pazopanib, sunitinib, imatinib, nilotinib, dasatinib and regorafenib) and two active metabolites (N-desmethyl imatinib and N-desethyl sunitinib) in human serum or plasma as described in **chapter 3**. This multi-TKI bioanalytical assay was successfully validated according to FDA guidelines. In comparison with the existing assays that determine multiple TKIs, we were the first to incorporate pazopanib and regorafenib [15-23]. This assay has been used for the clinical pharmacokinetic studies with pazopanib and sunitinib that are described in **chapter 5** and **chapter 6** of this thesis, respectively. In addition, this method is used in routine patient care to monitor and individualize the treatment with certain TKIs.

Monitoring of drug levels in serum or plasma makes sampling by venapuncture necessary. Sampling by dried blood spot (DBS) may be a more patient friendly alternative that can be performed at home. In **chapter 4** we studied the feasibility of DBS sampling to monitor pazopanib therapy. Thus far, the measurements of imatinib, nilotinib, dasatinib and dabrafenib in DBS have been described [24, 25]. However, focus of these studies was on assay development and validation, whereas our study focused on the next step towards clinical application; the agreement between pazopanib levels measured in plasma and calculated plasma concentrations from the corresponding DBS card. Results showed that these concentrations were in good agreement with each other and thus show the feasibility of measuring pazopanib concentrations on DBS cards in a clinical setting. Since DBS cards were prepared by the research nurse, validation of DBS cards prepared by patients remains necessary. However, we do not expected major problems as previously DBS samples prepared by patients have shown to be suitable for analysis [26, 27]. With the ease and convenience of sample

collection, DBS could be very useful to measure drug exposure in patients that are treated with pazopanib in an at home setting. If monitoring and dose optimization of oral targeted therapies is becoming more widespread, DBS will potentially also be of use for the measurement of other oral anticancer drugs that are mainly used in an at home setting.

Dose Optimization Strategies

A second goal of this thesis was to investigate the feasibility of dose optimization strategies for oral targeted therapies. The use of therapeutic drug monitoring (TDM) is one of such strategies. In **chapter 5** we investigated the feasibility of TDM to reduce the inter-patient variability in pazopanib exposure. The previously unreported high intra-patient variability in PK was the main reason why this study could not show the feasibility of TDM to reduce the inter-patient variability in exposure. Pazopanib intake was standardized to the advised use of pazopanib; 1 hour before or 2 hours after the intake of food as stated in the drug label. However, in the food interaction study that showed a 2-fold increase in exposure when pazopanib was administered with food, fasted was defined as no food intake for at least 8 hours [29]. Hence, the time interval of no food in our study was possibly insufficient to prevent an effect of food on pazopanib absorption. In addition, we did not standardize diet composition. A main lesson learned from this study is that, when there is an interaction of a particular drug with food (which is present for several TKIs), one should always keep in mind the interval of no food consumption and also try to standardize the composition of meals taken by patients. This is support by the preliminary results from two ongoing studies (NCT02138526 and NCT01995981) in which a much smaller intra-patient variability is found, most likely as a consequence of standardization of pazopanib intake in relation to food.

Recently, the final data that show an exposure-response relationship for pazopanib are reported [30]. These data indicate that the optimal window for pazopanib exposure is a C_{trough} level between 20.5 to 36 mg/L. Compared to the target window that we used in our study, this concentration window is much wider. Possibly, we might have been too stringent in our study. This is supported by the (preliminary) results from a study that also investigated the feasibility of PK-guided dosing of pazopanib [31]. This study was designed to reach a target $C_{trough} > 20$ mg/L. Dose modifications were based on measured C_{trough} levels as well as the grade of toxicity experienced. Of the patients with a $C_{trough} < 20$ mg/L that experienced no grade ≥ 3 toxicity, 40% achieved an exposure above the target at week 8 of treatment after dose modification. During study follow up this percentage was further increased to 70%. These results suggest that individualized dosing of pazopanib with the aim to reach a target C_{trough} level is feasible and leads to additional patients reaching the target exposure. Yet, prospective studies that show an effect on clinical outcome in terms of overall survival (OS) and progression free survival (PFS) are needed.

Next to TDM, another approach for dose optimization is the use of a non-invasive phenotyping probe in order to predict drug exposure before the start of therapy. In **Chapter 6** the feasibility of midazolam as a phenotyping probe for CYP3A4 activity to predict sunitinib exposure is described. The results of this study show that midazolam exposure was highly correlated with sunitinib exposure. This suggests that midazolam could be useful in clinical practice to identify those patients that are at risk for under- respectively overtreatment at the standard sunitinib dosage regimen. However, the suitability of an individualized dosing strategy for sunitinib based on phenotyping by midazolam would require prospective validation.

Explaining Inter-Patient Variability

The third goal of this thesis was to gain more knowledge of the underlying causes of the inter-patient variability in dug exposure of oral targeted therapies. The results of our phenotyping study suggest that half of the observed inter-patient variability in sunitinib PK can be explained by differences in CYP3A4 activity which is much more than earlier identified covariates [32, 33]. Phenotyping with midazolam possibly explains such a large percentage of the inter-patient variability in sunitinib pharmacokinetics because it represents the influence of both genetic differences as well as environmental covariates.

Patients with 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. Previous research has shown that imatinib and nilotinib C_{trough} levels were significantly lower in patients that previously had a major gastrectomy compared to patients without gastric surgery [34]. The suggested cause for this decreased exposure is the lack of gastric acid secretion in combination with poor solubility of imatinib and nilotinib at a pH above 5.5 and 4.5, respectively. Due to small differences in physicochemical properties, we hypothesized that a major gastrectomy would not have an influence on sunitinib exposure.

Indeed, as described in **chapter 7,** major gastrectomy alone did not influence the exposure to sunitinib or its active metabolite SU12662. We also found that patients with a combined gastrectomy and small bowel resection did have a statistically significantly decreased plasma exposure to sunitinib and its active metabolite. However, this observation was considered as clinically non relevant since exposures were still above

the threshold previously associated with sunitinib efficacy. Due to the retrospective character of our analysis, the length of intestine resected was unfortunately unknown. Theoretically, the influence of a combined gastrectomy and small bowel resection depends on the length of intestine resected and monitoring of sunitinib plasma concentrations is indicated in such situations.

The lack of an effect of major gastrectomy on sunitinib exposure, is in contrast to the results found for imatinib. This should be taken into account when treating gastrectomized GIST patients with TKIs. Hypothetically, gastrectomized patients have less and/or shorter treatment benefit from first-line imatinib therapy, when administered as a fixed dose, due to decreased imatinib plasma levels. Yet, these patients might have a high chance of benefit from second line sunitinib therapy. Another approach could be the administration of imatinib with an acidic containing beverage analogue to administration of, for example, itraconazol with coca cola when a proton pump inhibitor is used to increase exposure. This hypothesis is currently investigated in an ongoing study in the LUMC and Radboud UMC (NCT02185937). For now, depending on the type of resection of the GI tract, measuring exposure levels to imatinib, sunitinib and presumably also regorafenib could be helpful to decide whether there is sufficient exposure to these drugs.

In **chapter 8** we assessed the correlation between everolimus exposure and toxicity. Results show that patients who had their everolimus dose reduced due to toxicity, had significantly higher drug exposures than patients without reductions. Moreover, everolimus exposure was associated with the probability for stomatitis. Results were in line with findings from another study in patients with cancer [35]. The results of our study underscore the high inter-patient variability in everolimus PK as well as its correlation with toxicity. We should take this inter-patient variability, in combination with the growing evidence for a correlation between exposure and treatment efficacy and toxicity in the field of oncology, into account in the use of everolimus for the treatment of solid tumors. Future studies should first aim to clearly identify the optimum therapeutic window of everolimus exposure for different cancers. As TDM of everolimus is already the standard of care within transplantation medicine, dose individualization of everolimus in the field oncology is maybe not that far away.

Future Perspectives

Multiple opinion articles and reviews about the dose optimization of oral targeted therapies have been published in the last few years [36-48]. Next to the exposure-response relationship described in **chapter 2** which were published until February 2014, several new relationships have been shown [30, 49-52]. Furthermore, a few studies that investigated the feasibility of dose optimization to either reach a target exposure or reduce the inter-patient variability in PK have been conducted since then [31, 53-55]. Moreover, a recent study showed that about half of the plasma concentrations for imatinib, sunitinib and erlotinib in the outpatient population appear to be below their supposed target level [56]. However, thus far only one randomized controlled study that prospectively investigated the effect of imatinib TDM on clinical outcome has been published [57].

In this study, event free was defined as remaining without treatment failure, disease progression, occurrence of moderate clinical or severe laboratory adverse events or treatment discontinuation. In contrast to what was expected, this study could not demonstrate a benefit of TDM in terms of the percentage of patients that were event free. However, failure of this trial can be fully explained by the fact that adherence to dosage recommendations by prescribers was only 50% in the TDM arm. Of the patients that *did* receive the recommended TDM guided dose, 71% remained event free compared to 23% of the patients who did not or only partially received this recommended dose (absolute risk reduction 48%, $P = 0.033$). Therefore, I would like to oppose that this study actually does show us the beneficial effect of TDM to improve treatment outcome. Nevertheless, this study also highlights the challenges to prospectively investigate the benefit of TDM of targeted therapies on treatment outcome. Despite oral and written communication of dose recommendations, dose adjustments were not adhered to by the treating physician. Moreover, this study could only include 56 of the supposed 300 patients within the planned timeframe. Possibly, at present TDM does not belong as much to the culture of oncological patient care and is actually rarely used [37]. Hence, education about dose optimization within the field of oncology will become very important in the nearby future. This should lead to adequate patient recruitment and adherence to dose recommendations. Another challenge is the reimbursement by health insurances of the costs of administration of higher than registered doses of TKIs.

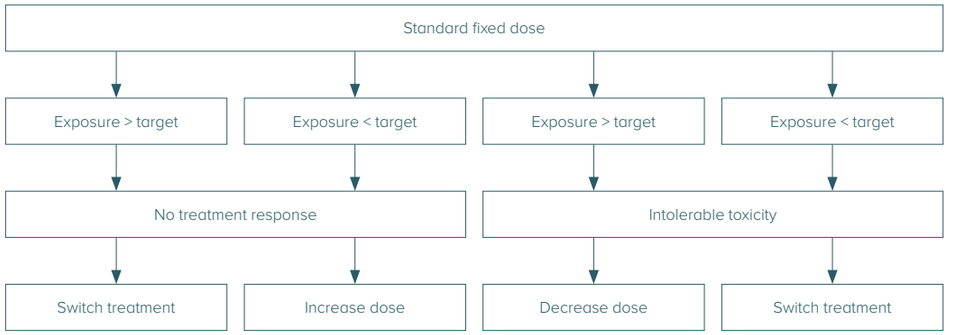
The main arguments for withholding dose optimization of oral targeted therapies from clinical practice are the lack of 1) studies that prospectively determine the relation between, or thresholds for, systemic drug exposure and treatment outcome and 2) studies that prospectively assess the influence of dose optimization on primary treatment outcome parameters both in terms of efficacy as well as toxicity. However, as long as the assessment of exposure-response relationships will not become a requirement by the regulatory agencies and the assessment of pharmacokinetics are not involved in phase III trials in which the efficacy of a new treatment is assessed, the lack of prospectively assessed correlations will remain.

As suggested by others, regulatory incentives for drug developers and healthcare providers maybe need to be put in place in order to generate forces that reward the exploration of exposure-response relationships and also dose optimization approaches [47]. At first it may seem that there are no apparent benefits for pharmaceutical companies to investigate dose optimization. However, actually it can be argued whether the failure of some clinical studies due to a lack of efficacy is possibly also a result of fixed dosing leading to under exposure of oral targeted therapies in a significant number of patients [42]. In addition, fixed dosing can lead to over exposure resulting in therapies that are effective but also extremely toxic in a significant number patients, such as everolimus and regorafenib.

Meanwhile, for oral targeted therapies that are already registered, retrospective data are the best we have and it can be discussed whether this is perhaps also good enough. In addition, it can be argued whether it is ethical to not measure since this means that we ignore the data on exposure-response relationships that we currently have. In my opinion and as also proposed by others, we should therefor just 'quit guessing and start measuring' [38]. Only by starting to measure, we can build comprehensive databases that can be used for further investigation of exposure-response relationships. Oral targeted therapies have different indications for sometimes small patient populations and exposure-response relationships should be defined separately per drug for each tumor type. Therefore, I believe that collaboration between research groups is of utmost importance. An example of such collaborations is the Dutch GIST consortium. Another novel example of such collaboration is the Dutch Pharmacology Oncology Group which aims at collaboration on dose optimization studies within oncology (www.dpog.nl).

As said, future research should focus on the added value of routine dose optimization strategies (such as TDM) of oral targeted therapies on clinical outcome to make dose optimization an evidence based approach. In my opinion, the thresholds defined by retrospective analysis could be used as target exposure for these dose optimization studies. With such an approach it can be tested at the same time within one study whether retrospectively defined correlations hold when prospectively investigated. Meanwhile, I suggest that the measurement of drug exposure is indicated in clinical practice in case of extreme or unexpected toxicity, a lack of expected clinical benefit, suspected PK drug-drug interactions, in patients with an altered anatomy of the GI tract or in case of suspected therapy nonadherence, to support clinical decision making for at least imatinib, sunitinib and pazopanib. Actually, the ESMO guideline for the diagnosis, treatment and follow-up of GIST recognizes the potential of measuring imatinib concentrations in these situations [58]. Recently, also the Dutch

Figure 1 Supposed dosing algorithm for future treatment with oral targeted therapies.
All patients start with the registered fixed dose of an oral targeted therapy. When steady-state is reached, exposures are measured. Based on exposure and clinical outcomes, the dose should be increased, decreased or a treatment switch should be made.



Association of Hospital Pharmacists published a document regarding TDM of imatinib [59]. This shows us that the dose optimization of oral targeted therapies is starting to become part of clinical practice. For targeted therapies without clearly defined thresholds, the average exposures identified in phase I or II trials on the registered dose could be used as second best alternative in specific circumstances.

Obviously, drug exposure is not the sole determinant of clinical outcome in patients with cancer and other factors such as patient- or tumor specific characteristics also contribute to the efficacy of oral targeted therapies. For different reasons, such as unnecessary toxicity, treatment delay, compliance, *de novo* inefficacy but also costs, it is crucial to identify those patients who are most likely to respond to oral targeted therapies. However, after selecting the most effective drug for a specific tumor type, dose individualization could further help to optimize the individual benefit-risk ratio, with the highest possible efficacy and the lowest possible toxicity of therapy.

In the future 'ideal, evidence based, dose optimized world', when we have more results from prospective randomized trials on dose optimization, dose adjustments and treatment switch are made according to the algorithm depicted in Figure 1. I expect that this strategy will lead to better treatment outcomes. Especially, since normally the dose of an oral targeted therapy is not increased when a patient does not show any toxic effects. However, this absence of toxicity is potentially also a sign of under exposure that could lead to treatment failure. On the other hand, in case

of toxicity the dose if often pragmatically lowered. However, for patients that already have exposures below the threshold associated with efficacy, a treatment switch to another therapy might be a better option compared to reducing the dose. I believe that in the 'ideal, evidence based, dose optimized world' drug exposure should be measured in all patients treated with oral targeted therapies. As said, this a future world and obviously trials that asses the feasibility of dose optimization on clinical outcome are warranted.

In 1892 Sir William Osler, a Canadian physician and one of the four founding professors of the Johns Hopkins Hospital, said: 'If it were not for the great variability among individuals, medicine might as well be a science, not an art'. He referred to the decisions that doctors make when prescribing medication as an art since objective data considering the benefits and harms on an individual patient level were lacking at that time. However, about one century later we should maybe reconsider these words as we are actually getting closer to a more evidence based approach for individualized treatments. This eventually should not only lead to the right drug for the right patient, but also to the administration of this drug in the right dose in order to achieve the right drug exposure level within each individual patient.

Conclusion

Future research should focus at showing the added value of dose optimization of oral targeted therapies on clinical outcome. The thresholds defined by either retrospective or future prospective analysis could be used as target exposure for these dose optimization studies Education about dose optimization within the field of oncology will become important in the nearby future both for the recruitment of trials as well as adherence to recommendations considering dosing. Meanwhile, the measurement of drug exposure seems justified in situations of extreme or unexpected toxicity, a lack of expected clinical benefit, suspected PK drug-drug interactions, in patients with major resections of the GI tract or in case of suspected therapy nonadherence, to support clinical decision making.

References

1 **Bai, F. et al** (2011) Determination of vandetanib in human plasma and cerebrospinal fluid by liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS). J Chromatogr B Analyt Technol Biomed Life Sci. 879, 2561-2566.

2 **Sparidans, R.W. et al** (2012) Liquid chromatography-tandem mass spectrometric assay for therapeutic drug monitoring of the tyrosine kinase inhibitor pazopanib in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 905, 137-140.

3 **Escudero-Ortiz, V. et al** (2015) Development and validation of an HPLC-UV method for pazopanib quantification in human plasma and application to patients with cancer in routine clinical practice. Ther Drug Monit. 37, 172-179.

4 **Etienne-Grimaldi, M.C. et al** (2009) A routine feasible HPLC analysis for the anti-angiogenic tyrosine kinase inhibitor, sunitinib, and its main metabolite, SU12662, in plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 877, 3757-3761.

5 **Lankheet, N.A. et al** (2013) Quantification of sunitinib and N-desethyl sunitinib in human EDTA plasma by liquid chromatography coupled with electrospray ionization tandem mass spectrometry: validation and application in routine therapeutic drug monitoring. Ther Drug Monit. 35, 168-176.

6 **Qiu, F. et al** (2012) Simultaneous determination of sunitinib and its two metabolites in plasma of Chinese patients with metastatic renal cell carcinoma by liquid chromatography-tandem mass spectrometry. Biomed Chromatogr.

7 **Rodamer, M. et al** (2011) Development and validation of a liquid chromatography/tandem mass spectrometry procedure for the quantification of sunitinib (SU11248) and its active metabolite, N-desethyl sunitinib (SU12662), in human plasma: application to an explorative study. J Chromatogr B Analyt Technol Biomed Life Sci. 879, 695-706.

8 **Sparidans, R.W. et al** (2009) Liquid chromatography-tandem mass spectrometric assay for the light sensitive tyrosine kinase inhibitor axitinib in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 877, 4090-4096.

9 **Sparidans, R.W. et al** (2012) Liquid chromatography-tandem mass spectrometric assay for the mutated BRAF inhibitor vemurafenib in human and mouse plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 889-890, 144-147.

10 **Sparidans, R.W. et al** (2013) Liquid chromatography-tandem mass spectrometric assay for the mutated BRAF inhibitor dabrafenib in mouse plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 925, 124-128.

11 **Wang, L.Z. et al** (2011) Rapid determination of gefitinib and its main metabolite, O-desmethyl gefitinib in human plasma using liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 879, 2155-2161.

12 **Zhao, M. et al** (2003) Specific method for determination of OSI-774 and its metabolite OSI-420 in human plasma by using liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 793, 413-420.

13 **Zhao, M. et al** (2005) Specific method for determination of gefitinib in human plasma, mouse plasma and tissues using high performance liquid chromatography coupled to tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 819, 73-80.

14 **Moes, D.J. et al** (2010) Liquid chromatography-tandem mass spectrometry outperforms fluorescence polarization immunoassay in monitoring everolimus therapy in renal transplantation. Ther Drug Monit. 32, 413-419.

15 **Lankheet, N.A. et al** (2012) Method development and validation for the quantification of dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, sorafenib and sunitinib in human plasma by liquid chromatography coupled with tandem mass spectrometry. Biomed Chromatogr.

16 **Chahbouni, A. et al** (2009) Simultaneous quantification of erlotinib, gefitinib, and imatinib in human plasma by liquid chromatography tandem mass spectrometry. Ther Drug Monit. 31, 683-687.

17 **de Francia, S. et al** (2009) New HPLC-MS method for the simultaneous quantification of the antileukemia drugs imatinib, dasatinib, and nilotinib in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 877, 1721-1726.

18 **Gotze, L. et al** (2012) Development and clinical application of a LC-MS/MS method for simultaneous determination of various tyrosine kinase inhibitors in human plasma. Clin Chim Acta. 413, 143-149.

19 **Haouala, A. et al** (2009) Therapeutic Drug Monitoring of the new targeted anticancer agents imatinib, nilotinib, dasatinib, sunitinib, sorafenib and lapatinib by LC tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 877, 1982-1996.

20 **Honeywell, R. et al** (2010) Simple and selective method for the determination of various tyrosine kinase inhibitors used in the clinical setting by liquid chromatography tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 878, 1059-1068.

21 **Hsieh, Y. et al** (2009) Hydrophilic interaction liquid chromatography/tandem mass spectrometry for the simultaneous determination of dasatinib, imatinib and nilotinib in mouse plasma. Rapid Commun Mass Spectrom. 23, 1364-1370.

22 **Couchman, L. et al** (2012) An automated method for the measurement of a range of tyrosine kinase inhibitors in human plasma or serum using turbulent flow liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem. 403, 1685-1695.

23 **Bouchet, S. et al** (2011) Simultaneous determination of nine tyrosine kinase inhibitors by 96-well solid-phase extraction and ultra performance LC/MS-MS. Clin Chim Acta. 412, 1060-1067.

24 **Kralj, E. et al** (2012) Simultaneous measurement of imatinib, nilotinib and dasatinib in dried blood spot by ultra high performance liquid chromatography tandem mass spectrometry. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences. 903, -156.

25 **Nijenhuis, C.M. et al** (2014) Quantifying vemurafenib in dried blood spots using high-performance LC-MS/MS. Bioanalysis. 6, 3215-3224.

26 **Cheung, C.Y. et al** (2008) Dried blood spot measurement: application in tacrolimus monitoring using limited sampling strategy and abbreviated AUC estimation. Transpl Int. 21, 140-145.

27 **Kromdijk, W. et al** (2013) Therapeutic drug monitoring of antiretroviral drugs at home using dried blood spots: a proof-of-concept study. Antivir Ther. 18, 821-825.

28 **Hurwitz, HI, et al.** Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res 2009;15:4220-7.

29 **Heath, E.I. et al** (2010) A phase I study of the pharmacokinetic and safety profiles of oral pazopanib with a high-fat or low-fat meal in patients with advanced solid tumors. Clin Pharmacol Ther. 88, 818-823.

30 **Suttle, A.B. et al** (2014) Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. Br J Cancer. 111, 1909-1916.

31 **Verheijen, R. et al** (2014) Individualized pharmacokinetically-guided dosing of pazopanib: a feasibility study in cancer patients. ESMO meeting 2014. Abstract 7651.

32 **Houk, B.E. et al** (2009) A population pharmacokinetic meta-analysis of sunitinib malate (SU11248) and its primary metabolite (SU12662) in healthy volunteers and oncology patients. Clin Cancer Res. 15, 2497-2506.

33 **Faivre, S. et al** (2006) Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol. 24, 25-35.

34 **Yoo, C. et al** (2010) Cross-sectional study of imatinib plasma trough levels in patients with advanced gastrointestinal stromal tumors: impact of gastrointestinal resection on exposure to imatinib. J Clin Oncol. 28, 1554-1559.

35 **Ravaud, A. et al** (2014) Relationship between everolimus exposure and safety and efficacy: meta-analysis of clinical trials in oncology. Eur J Cancer. 50, 486-495.

36 **Klumpen, H.J. et al** (2011) Moving towards dose individualization of tyrosine kinase inhibitors. Cancer Treat Rev. 37, 251-260.

37 **Josephs, D.H. et al** (2013) Clinical pharmacokinetics of tyrosine kinase inhibitors: implications for therapeutic drug monitoring. Ther Drug Monit. 35, 562-587.

38 **Gao, B. et al** (2012) Evidence for therapeutic drug monitoring of targeted anticancer therapies. J Clin Oncol. 30, 4017-4025.

39 **Yu, H. et al** (2014) Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. Clin Pharmacokinet. 53, 305-325.

40 **de Wit, D. et al** (2014) Individualized dosing of tyrosine kinase inhibitors: are we there yet? Drug Discov Today.

41 **Saez, M.I. et al** (2012) Practical guidelines for dose individualization of anticancer targeted drugs. Clin Transl Oncol. 14, 812-819.

42 **Bardin, C. et al** (2014) Therapeutic drug monitoring in cancer--are we missing a trick? Eur J Cancer. 50, 2005-2009.

43 **Paci, A. et al** (2014) Review of therapeutic drug monitoring of anticancer drugs part 1--cytotoxics. Eur J Cancer. 50, 2010-2019.

44 **Widmer, N. et al** (2014) Review of therapeutic drug monitoring of anticancer drugs part two--targeted therapies. Eur J Cancer. 50, 2020-2036.

45 **Miura, M.** (2015) Therapeutic drug monitoring of imatinib, nilotinib, and dasatinib for patients with chronic myeloid leukemia. Biol Pharm Bull. 38, 645-654.

46 **Judson, I.** (2012) Therapeutic drug monitoring of imatinib--new data strengthen the case. Clin Cancer Res. 18, 5517-5519.

47 **Beumer, J.H.** (2013) Without therapeutic drug monitoring, there is no personalized cancer care. Clin Pharmacol Ther. 93, 228-230.

48 **Petit-Jean, E. et al** (2015) Erlotinib: another candidate for the therapeutic drug monitoring of targeted therapy of cancer? A pharmacokinetic and pharmacodynamic systematic review of literature. Ther Drug Monit. 37, 2-21.

49 **Gotta, V. et al** (2014) Large-scale imatinib dose-concentration-effect study in CML patients under routine care conditions. Leuk Res. 38, 764-772.

50 **Noda, S. et al** (2015) Assessment of Sunitinib-Induced Toxicities and Clinical Outcomes Based on Therapeutic Drug Monitoring of Sunitinib for Patients With Renal Cell Carcinoma. Clin Genitourin Cancer.

51 **Cohen, E.E. et al** (2014) A Phase II trial of axitinib in patients with various histologic subtypes of advanced thyroid cancer: long-term outcomes and pharmacokinetic/pharmacodynamic analyses. Cancer Chemother Pharmacol. 74, 1261-1270.

52 **Locati, L.D. et al** (2014) Treatment of advanced thyroid cancer with axitinib: Phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. Cancer. 120, 2694-2703.

53 **Lankheet, N.A. et al** (2014) Pharmacokinetically guided sunitinib dosing: a feasibility study in patients with advanced solid tumours. Br J Cancer. 110, 2441-2449.

54 **de Wit, D. et al** (2014) Therapeutic Drug Monitoring to individualize the dosing of pazopanib: a pharmacokinetic feasibility study. Ther Drug Monit.

55 **Fujita, K. et al** (2014) High exposure to erlotinib and severe drug-induced interstitial lung disease in patients with non-small-cell lung cancer. Lung Cancer. 86, 113-114.

56 **Lankheet, N.A. et al** (2013) Plasma Concentrations of Tyrosine Kinase Inhibitors Imatinib, Erlotinib, and Sunitinib in Routine Clinical Outpatient Cancer Care. Ther Drug Monit.

57 **Gotta, V. et al** (2014) Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial. Cancer Chemother Pharmacol. 74, 1307-1319.

58 Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 25 Suppl 3, iii21-iii26.

59 **Moes-ten Hove J.E.and Wilhelm A.J.** (2014) TDM monografie imatinib. Nederlandse Vereniging voor Ziekenhuisapothekers, Commissie Analyse & Toxicologie.