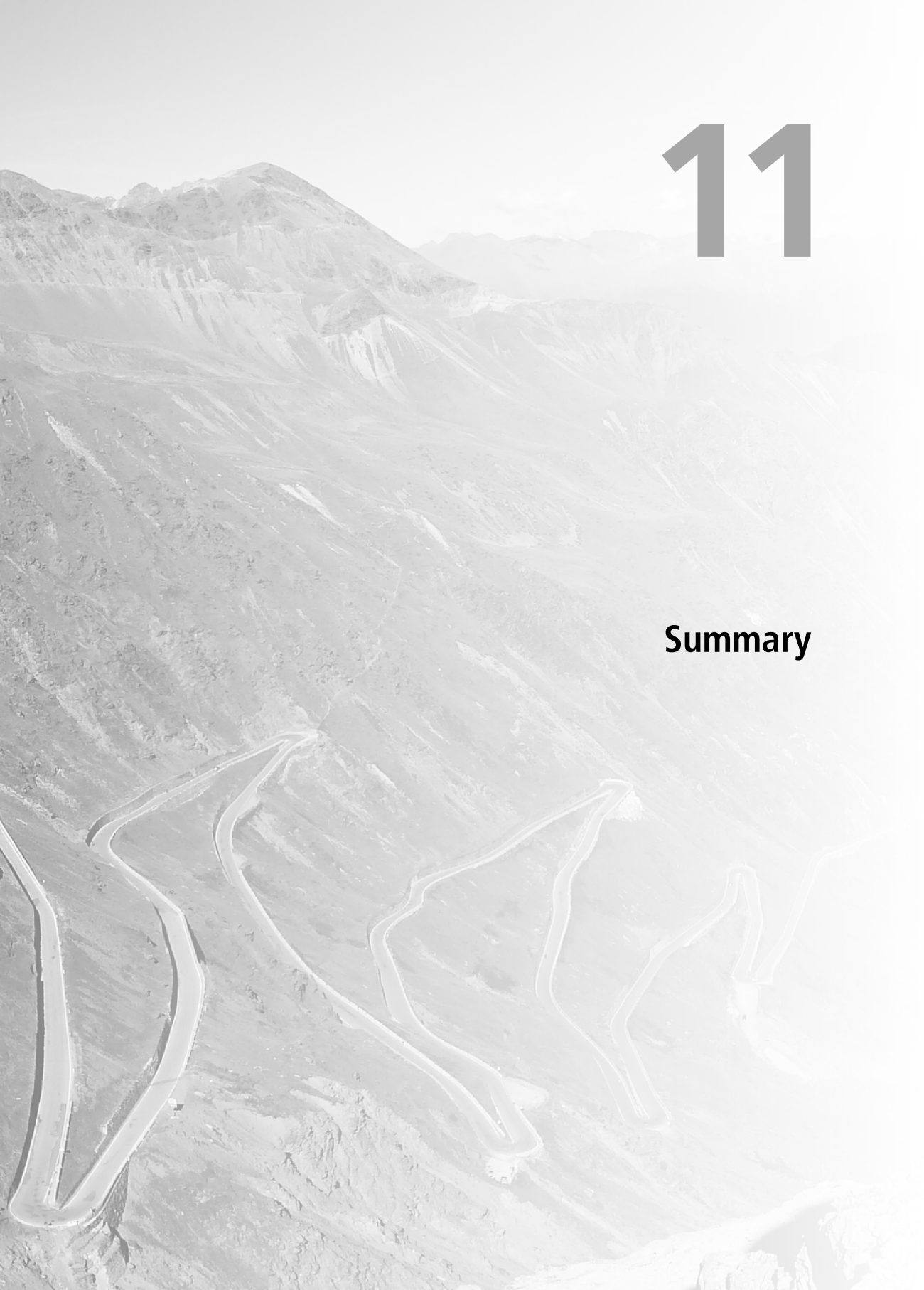

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Summary

Interpatient variability in drug disposition and response to anticancer agents challenges the clinician to individualize dose regimens in cancer patients. Selection of patients who will likely respond or will develop relevant side effects has the potential to improve anticancer therapy. Therapeutic drug monitoring (TDM) will be useful when there is a clear relationship between exposure of the drug and efficacy or toxicity. The use of TDM in the field of oncology is evolving since more and more assays for anticancer drugs become available. However, therapeutic windows for most anticancer agents have not been established thus far. When TDM is not available and a clear relationship exists between genotypic variants of metabolic enzymes and toxicity or response, genotype-guided dosing may be considered. Alternatively, the phenotype, comprising both the genotype and environmental factors, might be an alternative in case the anticancer drug displays a specific disposition for which a specific phenotype test is available. Considering the many contributing factors in drug disposition, we hypothesized that variability in drug disposition could be better explained by phenotype, rather than by the genotype alone. In this thesis, phenotype tests in oncology are studied, with a focus on phenotype breath tests and CYP2D6 metabolism in breast cancer patients using tamoxifen. Besides, we investigate whether factors such as the presence of metastases or frailty may alter the phenotype.

In **Chapter 2** a review is given of phenotype studies published before 2011 addressing drug metabolizing enzymes in relation to anticancer drugs. In the last decades, phenotype tests have been developed to easily and reliably assess drug disposition. The concept of such tests is the administration of a selective exogenous substrate (probe) for a specific enzyme or transporter and subsequently determination of pharmacokinetic parameters, such as absorption rate and the probe's complete or partial clearance over time. Despite the potential advantage of real-time determination of enzyme or drug transporter activity using *in vivo* the number of phenotype studies in oncology is limited to plus minus 20. Phenotype studies are often compromised by limited numbers of patients and poor correlation between probe and anticancer agent pharmacokinetics. Interpretation and extrapolation of results from phenotype studies are further limited by the use of intermediate endpoints such as correlation between probe and drug pharmacokinetic parameters. Despite the presence of these general limitations, **Chapter 3** gives an overview of some promising phenotype breath tests, such as the ^{13}C-dextromethorphan breath test (^{13}C-DM-BT) to phenotype CYP2D6 for prediction of tamoxifen efficacy and the ^{13}C-uracil breath test to predict dihydropyrimidine dehydrogenase (DPD)-deficiency related fluoropyrimidine toxicity in colorectal patients. However, clinical benefit and cost-effectiveness of these phenotype breath tests need to be determined in order to make the transition from experimental setting to clinical practice as companion diagnostic tests.

Chapter 4 specifically describes the ^{13}C-DM-BT to phenotype CYP2D6 in tamoxifen treated early breast cancer patients. The ^{13}C-DM-BT was related to CYP2D6 genotpe and serum concentrations of endoxifen, the active metabolite of tamoxifen. The breath test was equally predictive of endoxifen levels as compared to the CYP2D6 genotype. However, a direct prospective correlation between ^{13}C-DM-BT predicted CYP2D6 phenotype and tamoxifen efficacy is needed to explore its clinical relevance.

A large variation in the ^{13}C-DM-BT results was observed in the extensive metabolizer predicted phenotype group. **Chapter 5** describes the results of a pharmacokinetic study to characterize and to further improve the clinical utility of ^{13}C-DM-BT by introducing multiple breath sampling instead of a single breath sample and by administration of a fixed dose of ^{13}C-DM instead of a weight-based dose.

The presence of metastases in cancer patients might alter drug metabolism due to circulating interleukines. In **Chapter 6** the potential phenoconversion of CYP2D6 phenotype in metastasized breast cancer patients with extensive metabolizer CYP2D6 predicted phenotype is addressed. For this study, ^{13}C-DM-BT was used to determine CYP2D6 phenotype in tamoxifen early breast cancer patients versus metastasized breast cancer patients. We showed that there was no difference in CYP2D6 phenotype between metastasized patients and early breast cancer patients. Because endoxifen levels did not significantly differ between the two groups as well, our findings do not have clinical implications thus far.

When the CYP2D6 genotype or phenotype is proven to sufficiently predict tamoxifen efficacy, it might be possible to guide the tamoxifen dose based on CYP2D6 phenotype and/or endoxifen levels. **Chapter 7** describes the feasibility of TDM guided dosing of tamoxifen in patients with a CYP2D6 poor metabolizer (PM) and intermediate (IM) metabolizer phenotype. The tamoxifen dose was safely escalated up to 120 mg based on the individual endoxifen levels in patients using a standard dose of 20 mg tamoxifen. Despite the fact that no safety issues were observed in this study, it should be noted that sufficient data on long term risks and side effects of higher doses of tamoxifen are presently lacking.

Phenoconversion is a phenomenon that converts genotypic extensive metabolizers (EM) into phenotypic poor metabolizers (PM) of drugs. Cancer patients frequently have multiple comorbidities, which could affect disposition of anticancer agents. A specific disease state may alter drug metabolism as well. The presence of cytokines in the case of metastatic disease, such as IL6 and TNFα have been associated with reduced CYP1A2, CYP2C and CYP3A mediated

drug metabolism. In **Chapter 8** the results of the KINURA-2 study were presented, showing no difference in uracil pharmacokinetics, representing DPD phenotype, between colorectal patients with and without metastases. Phenoconversion seems to play no role in DPD phenotype in case of metastasized disease. Since DPD does not belong to the cytochrome P450 enzyme system, other mechanism of inhibition and induction may apply.

It is known that increased incidence of adverse drug reactions have been observed in frail elderly, which may be due to decreased drug metabolism related to frailty.

In **Chapter 9** we observed no phenoconversion however of CYP2D6 phenotype in frail elderly when compared to non-frail subjects. The results were in line with another study, in which CYP3A metabolism did not change with frailty. The increased incidence of adverse with frailty might therefore be related to other factors, such as altered drug-receptor interaction for example.