Treatment optimisation and pharmacogenetics of systemic and intraperitoneal chemotherapy in colorectal cancer

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SUMMARY

Colorectal cancer (CRC) is often treated with chemotherapy. However, it is well known that treatment with chemotherapy comes with challenges, such as (severe) adverse events leading to loss of quality of life, treatment discontinuation and sometimes even death. Moreover, chances for curation in the metastatic setting are low. Therefore, a large window of opportunity to improve both safety as well as efficacy of chemotherapeutic treatment for the individual patient exists. A possible approach to improve chemotherapeutic treatment for CRC patients could be the discovery, validation and implementation of new genetic biomarkers. The use of genetic biomarkers allows to identify patients that are at higher risk for severe adverse drug events and to select patients which will benefit the most from chemotherapy. The aim of this thesis was therefore to improve the safety and efficacy of chemotherapeutic drugs in patients with colorectal cancer by individualising drug dosing and choice of drug based on germline genetic biomarkers.

In Part I we focused on the optimisation of systemic treatment with irinotecan. We aimed to evaluate the added value and clinical utility of *UGT1A1* genotype-guided dosing of irinotecan by a systematic review of the literature and the development of a guideline on the drug-gene interaction between irinotecan and *UGT1A1*. For the ultimate evaluation we conducted a prospective implementation study on *UGT1A1* genotype-guided dosing of irinotecan.

In **Chapter 2** we assessed the available evidence and the potential value of *UGT1A1* genotype-guided dosing of irinotecan in order to reduce the risk of severe toxicity based on five pre-specified criteria, including: 1] the level of evidence for associations between *UGT1A1* polymorphisms and irinotecan-induced severe toxicity, 2] the clinical validity and utility of pre-therapeutic genotyping of *UGT1A1*, 3] the safety and tolerability of irinotecan in carriers of *UGT1A1* polymorphisms, 4] the availability of specific dose recommendations for irinotecan in carriers of *UGT1A1* polymorphisms, and 5] the evidence of cost benefits of pre-therapeutic genotyping of *UGT1A1*. On all five criteria, study results were favourable for pre-therapeutic genotyping of *UGT1A1*, namely: the highest level of evidence (level I) was found for a higher incidence of irinotecan-induced severe toxicity in homozygous carriers of *UGT1A1*28* or *UGT1A1*6* (UGT1A1 PMs); the clinical validity and utility of testing for *UGT1A1*28* or *UGT1A1*6* proved to be acceptable; dose-finding studies showed a lower maximum tolerated dose in homozygous variant allele carriers; and most of the drug labels and guidelines recommend a dose reduction of 25 to 30% in these patients. Also, pre-therapeutic genotyping of UGT1A1 is likely cost-saving.

In **Chapter 3** we aimed to facilitate implementation of UGT1A1 genotype guided dosing of irinotecan by writing a guideline – on behalf of the Dutch Pharmacogenetics Working Group (DPWG)

– for physicians and pharmacists, based on a systematic review of the literature on *UGT1A1* genotype-guided dosing of irinotecan. As also has been reported in **Chapter 2**, for UGT1A1 PMs there is ample evidence for an increased risk of serious adverse events such as neutropenia or diarrhoea at normal doses (also when compared to all other genotypes/phenotypes), while convincing evidence for an increased efficacy has not been demonstrated. All nine meta-analyses investigating adverse events, and 16 of the 23 included studies reported this increased risk of toxicity. With regard to efficacy, four of the five meta-analyses and eight of the ten studies did not show the *28 and/or *6 variants to be associated with increased effectiveness of treatment. Based on pharmacokinetic studies, this DPWG guideline recommends a 70% starting dose in UGT1A1 PM patients that start treatment with irinotecan. In UGT1A1 intermediate metaboliser patients, an a priori dose reduction is not recommended. Based on the DPWG clinical implication score, *UGT1A1* genotyping is considered "essential", therefore directing towards pre-therapeutic *UGT1A1* testing in patients intended for treatment with irinotecan.

Chapter 4, describes the first prospective implementation study on *UGT1A1* genotype-guided dosing of irinotecan. In this chapter, *UGT1A1* genotype-guided dosing of irinotecan was implemented in clinical practice. We demonstrated that genotype-guided dosing significantly reduced the incidence of febrile neutropenia and chemotherapy-related hospital admissions in UGT1A1 PMs. Of the 350 evaluable patients, 31 (8.9%) patients were UGT1A1 PM and received a median 30% dose reduction. The incidence of febrile neutropenia in this group was 6.5% compared to 24% in historical UGT1A1 PMs (p=0.04) and was comparable to the incidence in UGT1A1 non-PMs treated with full dose therapy. Systemic exposure of SN-38 of reduced dosing in UGT1A1 PMs was still slightly higher compared to a standard-dosed irinotecan patient cohort (difference: +32%). Cost analysis showed that genotype-guided dosing was cost-saving with a cost reduction of €183 per patient. This chapter showed that *UGT1A1* genotype-guided dosing of irinotecan significantly improves patient safety without a risk of underdosing. As a result, *UGT1A1* genotype-guided dosing was successfully implemented in four hospitals in the Netherlands and we highly recommend to implement this in clinical practice.

In **Part II**, we focused on the optimisation of intraperitoneal chemotherapy in patients with colorectal peritoneal metastasis. We aimed to identify genetic biomarkers predictive for treatment outcome of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS + HIPEC).

To do so, in **Chapter 5** we first conducted a systematic review of the literature on the association of genetic biomarkers in the DNA repair pathway and treatment outcome of patients

treated with CRS + HIPEC. As HIPEC agents we included both oxaliplatin or mitomycin C. Since literature on intraperitoneal chemotherapy and genetic biomarkers was scarce, we expanded our search strategy to systemic chemotherapy. In total, 43 papers were included in this review. No study reported potential pharmacogenomic biomarkers in patients with colorectal cancer undergoing MMC-based systemic chemotherapy. For oxaliplatin-based systemic chemotherapy, a total of 26 genetic biomarkers within 14 genes were identified that were significantly associated with treatment outcome. The most promising genetic biomarkers were *ERCC1* rs11615, *XPC* rs1043953, *XPD* rs13181, *XPG* rs17655, *MNAT* rs3783819/rs973063/rs4151330, MMR status, ATM protein expression, *HIC1* tandem repeat D17S5 and *PIN1* rs2233678. By extrapolation, these genetic biomarkers may also be predictive for the efficacy of intraperitoneal oxaliplatin. This should be the subject of further investigation.

In **Chapter 6** we conducted a retrospective genome-wide association study in a CRC patient cohort of 258 patients consecutively treated with CRS + HIPEC in order to identify new genetic biomarkers potentially associated with treatment outcome. The study revealed twelve markers that were significantly associated with reduced disease-free survival (DFS), which influence the expression of six genes. For four out of these six identified genes (*FAM3B*, *STAG1*, *SCL35G2*, and *METTL22*) one or more biological mechanisms could be identified that are in support of the observed associations of the genetic biomarkers with reduced DFS. Several new potentially prognostic or predictive genetic biomarkers for clinical outcome of CRS-HIPEC patients were identified. This is the first GWAS study in this type of patient population, and before clinical application of these findings the data require further validation in an independent patient cohort.

In **Chapter 7** we aimed to provide a proof of principle. We conducted a retrospective, hypothesis-driven study, in which *NQO1*2*, *NQO1*3*, and *POR*28* as possible genetic biomarkers for hyperthermic intraperitoneal mitomycin C were clinically validated. As a prodrug, mitomycin C requires metabolic activation prior to exert its cytotoxic effect, of which the main activating enzymes are NQO1 and POR. However, not all patients are able to activate mitomycin C, for example due to polymorphisms in the genes encoding these enzymes. The aim of this study was to investigate the association of *NQO1*2*, *NQO1*3*, and *POR*28* with the efficacy of CRS plus HIPEC with mitomycin C in patients with colorectal peritoneal metastasis. In this retrospective study, a total of 253 patients were included. Carriership of *NQO1*3* was associated with worse peritoneal recurrence rate, the peritoneal recurrence rate 3 and 6 months after HIPEC was significantly higher than in wild type patients, respectively 30.0% versus 3.8% (p=0.009) and 40.0% versus 12.1% (p=0.031). In line with these results, *NQO1*3* carriership

was associated with a shorter DFS (HR 2.04, 95% CI [1.03–4.03]). There was no significant association with overall survival (HR 1.42, 95% CI [0.66–3.07]). These results suggest that individualisation of patients treated with CRS plus HIPEC based upon pharmacogenetics may be beneficial and should be subject of further investigation.

In **conclusion**, the described studies in this thesis brought us a few steps closer to safe and effective use of chemotherapeutic drugs in the individual colorectal cancer patient. Irinotecan should no longer be administered without a UGT1A1 genotype test and a start has been made towards personalised medicine for colorectal cancer patients with peritoneal metastases.