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

Hulshof, E.C.

CHAPTER 8

General discussion

Colorectal cancer (CRC) is a widespread disease for which one of the main treatment modalities is chemotherapy. Chemotherapeutic treatment comes with challenges, such as severe adverse events leading to loss of quality of life, treatment discontinuation and sometimes even toxic death. In addition, chances for curation in the metastatic setting are low. Therefore, there is a window of opportunity to improve safety and efficacy of chemotherapeutic treatment of CRC for the individual patient.

The studies described in this thesis aimed 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. Within this last chapter, the findings are discussed in a broader perspective and potential clinical implications and future perspectives are provided.

PART I

In **Part I** of this thesis we aimed to implement *UGT1A1* genotype-guided dosing of irinotecan in clinical practice. We showed that the combined conclusion of multiple dose-finding studies indicate that the current standard way of dosing of irinotecan is not safe for UGT1A1 poor metaboliser patients (UGT1A1 PM patients) [1]. Therefore, the DPWG provided a dose recommendation for UGT1A1 PM patients, an initial dose reduction of irinotecan of 30% [1]. This 30% dose reduction for UGT1A1 PM patients was implemented in clinical practice and hereby we proved that this is feasible and a safe starting dose with adequate systemic exposure of the active metabolite SN-38 [2]. The incidence of febrile neutropenia and chemotherapy-related hospital admissions in UGT1A1 PM patients was significantly reduced. *UGT1A1* genotype-guided dosing of irinotecan proved to be feasible in daily practice as there was no delay in start of treatment. Moreover, it proved to be cost-saving compared to non-screening, with a total saving of €183 per patient.

All taken together, *UGT1A1* genotype-guided dosing was successfully implemented in four hospitals in the Netherlands. This thesis has led to acceptance of *UGT1A1* genotype-guided dosing of irinotecan as a new standard of care in the field of oncology in the Netherlands, approximately 70% of the medical oncologists would like to implement *UGT1A1* genotype-guided dosing of irinotecan. This number is based on a survey that was held at a post-ASCO congress in 2021 by the Dutch Society of Medical Oncology.

Wider implementation of *UGT1A1* genotype-guided dosing of irinotecan provides an opportunity for assessment of further efficacy outcomes and this might lead to further incorporation of *UGT1A1* genotype-guided dosing of irinotecan in clinical treatment guidelines, one of the main challenges in the near future. In addition, it is important to point out four other challenges to further personalise CRC treatment with irinotecan.

First, in our study we adapted the dose of irinotecan in UGT1A1 PM patients [3]. No dose adaptations were made in UGT1A1 intermediate metaboliser (IM) and extensive metaboliser (EM) patients. However, literature data suggest that safety-wise it seems possible to escalate the irinotecan dose in UGT1A1 EM patients which might lead to a higher efficacy in these patients [1]. Also, in our study subgroup analysis we noted that the incidence of severe irinotecan-related toxicity in EM patients was lower compared to IM patients which provides an additional argument for dose escalation studies in EM patients [3]. Therefore, further research on clinical efficacy outcomes of irinotecan dose escalation in EM patients is warranted.

Secondly, in our study we did not report on the *UGT1A1*6* variant allele and therefore we excluded patients of Asian origin but the *6 variant allele is also important in this population [4, 5]. The effect of the *6 variant allele on UGT1A1 functionality is comparable to the effect of *28 on UGT1A1 functionality [6]. Therefore, for the Asian population, it is of importance to not only incorporate the *UGT1A1*28* variant in clinical practice, but also the *6 variant. This test should not only be available to patients of Asian origin living in Asian countries, but also to patients of Asian origin in the Netherlands.

Thirdly, although *UGT1A1* genotype-guided dosing showed to reduce severe toxicity, patients may still encounter severe adverse advents such as late onset diarrhoea. Therefore, it is of importance to identify other biomarkers that are predictive for irinotecan-induced severe diarrhoea and to incorporate these in clinical practice. There are two interesting hypotheses that need further research. First, a genetic biomarker that seems a promising predictor of irinotecan-induced severe diarrhoea is *ABCB1* rs1128503. The *ABCB1* gene encodes for P-glycoprotein (P-gp), an ATP-mediated transporter that participates in the biliary excretion of irinotecan and SN-38. It is hypothesized that enhanced P-gp expression increases biliary secretion of SN-38 and thereby increases the risk of severe diarrhoea [7]. Second, it is hypothesized that high activity of the gut microbiota-derived enzyme β-glucuronidase (GUS) will be associated with increased late-onset gastrointestinal activation of SN38-G back to SN38 and thereby leading to irinotecan related-diarrhoea [8, 9]. At the same time, interpatient variability of these gut microbiota-derived GUS enzymes is high, in a sample of 139

individuals a high variability in the number of different GUS enzymes was observed ranging from a minimum of 4 to a maximum of 38 per individual [10]. It is hypothesized that possible targeted interventions such as the use of prebiotic compounds, fecal transplant therapy or antibiotics in selected patient with high GUS activity could reduce the risk of irinotecan-related late onset diarrhoea [8, 9].

Fourthly, with regard to clinical and biological characteristics, CRC is a very diverse illness, resulting in a high variability in disease development and treatment response and therefore calls for a personalised treatment. This has led to the development of the consensus molecular subtypes (CMS) of CRC, a well-studied and robust stratification strategy. CRC can be categorised into four subtypes (CMS1-4) based on differences in gene expression in tumour tissue, which includes both cancer cells and the microenvironment. This tumour molecular profiling by means of CMS classification can potentially predict the efficacy of irinotecan-based systemic therapy. Several studies have reported that irinotecan based-regimens rather than oxaliplatin based-regimens seem to be more effective in metastatic CRC CMS subtypes 1 and 4. Therefore it is of great importance to further investigate this possible biomarker for treatment selection because the first-choice regimen in the first-line setting often is oxaliplatin based [11].

PART II

In **Part II** we aimed to discover genetic biomarkers that are predictive for treatment outcome of colorectal peritoneal metastases patients treated with CRS + HIPEC. It appeared that only two studies investigated the association of biomarkers related to DNA repair and treatment outcome of CRS + HIPEC with mitomycin C or oxaliplatin [12]. However, in patients with colorectal cancer that were treated with intravenously administered oxaliplatin, a clear association between genetic biomarkers in the DNA repair pathway and treatment outcome was reported in literature. Therefore, we conducted a genome-wide association analysis and several genetic biomarkers were identified that were significantly associated with disease-free survival and/or survival in CPM patients that were treated with CRS + HIPEC [13]. In addition, a proof of principle was provided [14]. We hypothesized that patients with reduced activation capacity by NQO1 or POR due to a genetic polymorphism have a decreased response to MMC chemotherapy in the CRS + HIPEC setting. The aim of this candidate gene study was to investigate the association of *NQO1*2*, *NQO1*3*, and *POR*28* with the efficacy of CRS + HIPEC treatment with MMC in patients with CPM. In line with the hypothesis, a

clear association was observed between the *NQO1*3* polymorphism treatment outcome in patients treated with CRS+ HIPEC with mitomycin C. This study shows that pharmacogenetic biomarkers may potentially be useful for treatment selection in this population. However, our exploratory data first need to be confirmed. This was a candidate gene driven approach, potentially also other pharmacogenetic biomarkers within the PK/PD pathway may further explain interpatient variability in treatment response.

Thereby, **Part II** points us further towards the prognostic and/or predictive value of genetic biomarkers for CRS plus HIPEC treatment outcome. However, the amount of evidence is still scarce. Therefore, there is a need for replication studies to validate the genetic biomarkers that were identified. In addition, it would be of great interest to further distinct between the prognostic or predictive effect of these biomarkers. Our patient cohort only consisted out of CPM patients that were treated with CRS + HIPEC, we had no untreated cohort available which is required to conclude whether a genetic biomarker is predictive for treatment outcome [15].

In addition, the genetic biomarkers that were identified all have a low minor allele frequency and therefore a limited clinical relevance in the total patient population. This power to estimate and individual's phenotype based on genotype data can potentially be improved by the introduction of a polygenic risk score. A polygenic risk score can be defined as: "a single value estimate of an individual's common genetic liability to a phenotype, calculated as a sum of their genome-wide genotypes, weighted by corresponding genotype effect size estimates derived from summary statistic GWAS data" [16]. The development of this score seems a worthwhile step from GWA studies towards precision medicine in clinical practice.

In conclusion, the described studies 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.

REFERENCES

[1] Hulshof EC, Deenen MJ, Guchelaar HJ, Gelderblom H. Pre-therapeutic UGT1A1 genotyping to reduce the risk of irinotecan-induced severe toxicity: Ready for prime time. Eur J Cancer 2020;141:9–20. https://doi.org/10.1016/j.ejca.2020.09.007.

[2] Hulshof EC, Deenen MJ, Nijenhuis M, Soree B, de Boer-Veger NJ, Buunk AM, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene drug interaction between UGT1A1 and irinotecan. Eur J Hum Genet, under review, 2022.

[3] Hulshof EC, de With M, de Man FM, Creemers GJ, Deiman BALM, Swen JJ, et al. UGT1A1 genotype-guided dosing of irinotecan: A prospective safety and cost analysis in poor metaboliser patients. Eur J Cancer 2022;162:148–57. https://doi.org/10.1016/j.ejca.2021.12.009.

[4] Han FF, Guo CL, Yu D, Zhu J, Gong LL, Li GR, et al. Associations between UGT1A1*6 or UGT1A1*6/*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients. Cancer Chemother Pharmacol 2014;73:779–88. https://doi.org/10.1007/s00280-014-2405-0.

[5] Cheng L, Li M, Hu J, Ren W, Xie L, Sun ZP, et al. UGT1A1*6 polymorphisms are correlated with irinotecan-induced toxicity: A system review and meta-analysis in Asians. Cancer Chemother Pharmacol 2014;73:551–60. https://doi.org/10.1007/s00280-014-2382-3.

[6] Minami H, Sai K, Saeki M, Saito Y, Ozawa S, Suzuki K, et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: Roles of UGT1A1*6 and *28. Pharmacogenet Genomics 2007;17:497–504. https://doi.org/10.1097/FPC.0b013e328014341f.

[7] Riera P, Artigas-Baleri A, Salazar J, Sebio A, Virgili AC, Arranz MJ, et al. ABCB1 Genetic Variants as Predictors of Irinotecan-Induced Severe Gastrointestinal Toxicity in Metastatic Colorectal Cancer Patients. Front Pharmacol 2020;11:973. https://doi.org/10.3389/FPHAR.2020.00973/BIBTEX.

[8] Bhatt AP, Pellock SJ, Biernat KA, Walton WG, Wallace BD, Creekmore BC, et al. Targeted inhibition of gut bacterial β-glucuronidase activity enhances anticancer drug efficacy. Proc Natl Acad Sci U S A 2020;117:7374–81. https://doi.org/10.1073/PNAS.1918095117/-/DCSUPPLEMENTAL.

[9] Yue B, Gao R, Wang Z, Dou W. Microbiota-Host-Irinotecan Axis: A New Insight Toward Irinotecan Chemotherapy. Front Cell Infect Microbiol 2021;11:980. https://doi.org/10.3389/FCIMB.2021.710945/BIBTEX.

[10] Pollet RM, D'Agostino EH, Walton WG, Xu Y, Little MS, Biernat KA, et al. An Atlas of β-Glucuronidases in the Human Intestinal Microbiome. Structure 2017;25:967. https://doi.org/10.1016/J.STR.2017.05.003.

[11] Hoorn S Ten, De Back TR, Sommeijer DW, Vermeulen L. Clinical Value of Consensus Molecular Subtypes in Colorectal Cancer: A Systematic Review and Meta-Analysis. J Natl Cancer Inst 2022;114:503–16. https://doi.org/10.1093/JNCI/DJAB106.

[12] Hulshof EC, Lim L, de Hingh IHJT, Gelderblom H, Guchelaar H-J, Deenen MJ. Genetic Variants in DNA Repair Pathways as Potential Biomarkers in Predicting Treatment Outcome of Intraperitoneal Chemotherapy in Patients With Colorectal Peritoneal Metastasis: A Systematic Review. Front Pharmacol 2020;11:577968. https://doi.org/10.3389/fphar.2020.577968.

[13] Hulshof EC, Böhringer, S, van de Vlasakker VCJ, Wortman J, Lurvink RJ, de Hingh IHJT, et al. Genome-wide association study for predictors of survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with colorectal peritoneal metastases, this thesis, 2022.

[14] Hulshof EC, Lurvink RJ, Caserta N, de Hingh IHJT, van Wezel T, Böhringer S, et al. Identification of pharmacogenetic biomarkers for efficacy of cytoreductive surgery plus hyperthermic intraperitoneal mitomycin C in patients with colorectal peritoneal metastases. Eur J Surg Oncol 2020;46:1925–31. https://doi.org/10.1016/j.ejso.2020.04.019.

[15] Ballman KV. Biomarker: Predictive or prognostic? J Clin Oncol 2015;33:3968–71. https://doi.org/10.1200/JCO.2015.63.3651.

[16] Choi SW, Mak TSH, O'Reilly PF. A guide to performing Polygenic Risk Score analyses. Nat Protoc 2020;15:2759. https://doi.org/10.1038/S41596-020-0353-1.