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

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# CHAPTER 1

General introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both males and females in the Netherlands. In 2021, nearly 13,000 patients were newly diagnosed with CRC and the mortality was 4,500 [1]. Approximately 20% of the patients have metastatic disease at the primary diagnosis of CRC [1]. Another approximately 20% develop metastatic disease later on [2]. The most common metastatic sites are the liver, the peritoneum and the lungs. Chances for curation in the metastatic setting of CRC are still low with a 5-years survival of only 12% [1]. Especially in patients with colorectal peritoneal metastasis, survival is found to be worse compared to patients with metastatic disease at other distant sites [3].

In the Netherlands, most patients without distant metastasis undergo surgery (95%). Besides surgery, chemotherapy is one of the CRC treatment modalities, especially in the treatment of advanced and metastatic disease. In total, 61% of the stage III colon cancer patients undergo treatment with adjuvant chemotherapy. In addition, 50% of the patients with distant metastatic disease (stage IV) undergo palliative chemotherapy treatment. [1] 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, there is a large window of opportunity to improve both safety as well as efficacy of chemotherapeutic treatment for the individual patient.

## GENETIC BIOMARKERS

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. For example, a genotype test that was recommended in 2020 by the European Medicines Agency in order to prevent severe adverse events and even fatal toxicity during fluoropyrimidines treatment was pre-therapeutic genotyping of DPYD in patients treated with fluoropyrimidines [4]. This has led to wider implementation of this upfront genotype test, and has brought us a step closer to personalised medicine and safer dosing of chemotherapy [5].

## IMPLEMENTATION OF GENETIC BIOMARKERS

Another genetic biomarker that seems very promising in preventing severe adverse drug events in patients treated with irinotecan is UGT1A1 **28*. Irinotecan is frequently prescribed in patients with metastatic colorectal cancer or pancreatic cancer. Irinotecan is a prodrug that is activated via carboxylesterases in the liver and blood to SN38, which in turn is glucuronidated by UDP-glucuronosyltransferase 1A1 (UGT1A1) in the liver and intestines into SN38-glucuronide (SN38-G). UGT1A1 is the main enzyme responsible for the inactivation of SN38. Genetic variance in the *UGT1A1* gene leads to a decreased activity of the UGT1A1 enzyme [6]. More specific, the *UGT1A1**28 variant leads to a 18–33% reduced expression of *UGT1A1*, which in turn leads to higher SN-38 levels and a hence a higher risk of severe adverse drug events in patient carrying this variant allele [7].

While there is ample evidence in the literature on the association between *UGT1A1*28* and severe toxicity of irinotecan [8, 9] – yet – *UGT1A1* genotyping is not being routinely applied. Therefore, in the first part of this thesis we aim to implement *UGT1A1* genotype-guided dosing of irinotecan in clinical practice.

## DISCOVERY AND VALIDATION OF GENETIC BIOMARKERS

Prior to implementation, discovery and validation of new genetic biomarkers is essential. This is especially true for the colorectal peritoneal metastasis population, since survival in patients with colorectal peritoneal metastasis is less favourable compared to patients with other metastatic CRC. The current treatment of colorectal peritoneal metastasis is cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS + HIPEC), which has already brought a major gain in survival compared to palliative chemotherapy only [10, 11]. HIPEC was added to CRS in order to minimise invisible residual cancer in the peritoneum. However, CRS + HIPEC treatment is not without complications; around 20–40% of the patients experience severe complications and the treatment-related mortality is 3% [12–14]. Moreover, many patients still experience recurrent (peritoneal) disease. A possible solution for this problem would be the use of genetic biomarkers to predict which patients benefit the most from hyperthermic intraperitoneal mitomycin C or oxaliplatin. Therefore, in part II of this thesis we aim to discover genetic biomarkers that are predictive for treatment outcome of colorectal peritoneal metastasis patients treated with CRS + HIPEC.

In short, in this thesis we aim 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. The studies presented in this thesis address the following research questions:

**Part I: Implementation of *UGT1A1* genotype-guided dosing of irinotecan**

- What is the potential value of *UGT1A1* genotype-guided dosing of irinotecan? What is the level of evidence?
- What is the optimal starting dose of irinotecan per *UGT1A1* genotype?
- Is *UGT1A1* genotype-guided dosing of irinotecan less toxic and just as effective as standard dosing of irinotecan in clinical practice?
- Is *UGT1A1* genotype-guided dosing of irinotecan feasible and cost-effective in clinical practice?

**Part II: Discovery and validation of genetic biomarkers for hyperthermic intraperitoneal chemotherapy (HIPEC)**

- Are genetic biomarkers in the DNA repair pathway associated with treatment outcome of patients treated with CRS + HIPEC with oxaliplatin or mitomycin C?
- Can we identify new genetic biomarkers that are predictive for CRS + HIPEC treatment outcome?
- Are the genetic biomarkers *NQO1*2*, *NQO1*3*, and *POR*28* associated with the efficacy of CRS + HIPEC treatment with mitomycin C?

**Part I** describes the added value and clinical utility of *UGT1A1* genotype-guided dosing of irinotecan. In **Chapter 2** an overview of the available evidence on *UGT1A1* genotype-guided dosing of irinotecan is provided. **Chapter 3** provides a guideline on *UGT1A1* genotype-guided dosing of irinotecan. With this guideline we aim to aid physicians and pharmacists in the implementation of *UGT1A1* genotype-guided dosing of irinotecan. **Chapter 4** describes a prospective trial on *UGT1A1* genotype-guided dosing of irinotecan in which the safety, feasibility and costs of this strategy is investigated. This pivotal study should provide the evidence whether or not *UGT1A1* genotype-guided dosing of irinotecan should be the new golden standard.

In **Part II** an exploration on genetic biomarkers for the treatment outcome of CRS + HIPEC is described. **Chapter 5** gives an overview of the available literature on the association of genetic biomarkers in the DNA repair pathway and treatment outcome of patients treated with

oxaliplatin or mitomycin C. **Chapter 6** describes a retrospective genome-wide association study on a CRS + HIPEC patient cohort, in order to identify new genetic biomarkers that are associated with treatment outcome. **Chapter 7** describes a retrospective, hypothesis-driven study, in which possible genetic biomarkers for hyperthermic intraperitoneal mitomycin C, based on previous preclinical findings, are clinically validated.

This thesis concludes with a general discussion and future perspectives in **Chapter 8**. Summaries of this thesis in both English and Dutch are presented in **Chapters 9** and **10**.

## REFERENCES

[1] Cijfers darmkanker n.d. https://iknl.nl/kankersoorten/darmkanker/registratie (accessed May 16, 2022).
[2] van Gestel YRBM, de Hingh IHJT, van Herk-Sukel MPP, van Erning FN, Beerepoot L V., Wijsman JH, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiol 2014;38:448–54. https://doi.org/10.1016/J.CANEP.2014.04.004.
[3] van der Geest LGM, Lam-Boer J, Koopman M, Verhoef C, Elferink MAG, de Wilt JHW. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clin Exp Metastasis 2015;32:457–65. https://doi.org/10.1007/S10585-015-9719-0.
[4] ESMO. EMA Provides New Testing and Treatment Recommendations for Fluorouracil Capecitabine and Tegafur 2020. https://www.esmo.org/oncology-news/ema-provides-new-testing-and-treatment-recommendations-for-fluorouracil-capecitabine-and-tegafur (accessed April 10, 2020).
[5] Henricks PharmD LM, Meulendijks PharmD D, M Schellens JH, Henricks LM, T C Lunenburg CA, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. Lancet Oncol 2018;19:1459–67. https://doi.org/10.1016/S1470-2045(18)30686-7.
[6] de Man FM, Goey AKL, van Schaik RHN, Mathijssen RHJ, Bins S. Individualization of Irinotecan Treatment: A Review of Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics. Clin Pharmacokinet 2018;57:1229–54. https://doi.org/10.1007/s40262-018-0644-7.
[7] Bosma PJ, Chowdhury JR, Bakker C, Gantla S, de Boer A, Oostra BA, et al. The Genetic Basis of the Reduced Expression of Bilirubin UDP-Glucuronosyltransferase 1 in Gilbert's Syndrome. N Engl J Med 1995;333:1171–5. https://doi.org/10.1056/nejm199511023331802.
[8] Liu X, Cheng D, Kuang Q, Liu G, Xu W. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: A meta-analysis in Caucasians. Pharmacogenomics J 2014;14:120–9. https://doi.org/10.1038/tpj.2013.10.
[9] Yang Y, Zhou MM, Hu M, Cui Y, Zhong Q, Liang L, et al. UGT1A1*6 and UGT1A1*28 polymorphisms are correlated with irinotecan-induced toxicity: A meta-analysis. Asia Pac J Clin Oncol 2018;14:e479–89. https://doi.org/10.1111/ajco.13028.
[10] Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737–43. https://doi.org/10.1200/JCO.2003.04.187.

[11] Verwaal VJ, Bruin S, Boot H, Van Slooten G, Van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15:2426–32. https://doi.org/10.1245/S10434-008-9966-2.

[12] Simkens GA, Rovers KP, Van Oudheusden TR, Nienhuijs SW, Rutten HJ, De Hingh IH. Major influence of postoperative complications on costs of cytoreductive surgery and HIPEC in patients with colorectal peritoneal metastases. Med (United States) 2018;97. https://doi.org/10.1097/MD.0000000000010042.

[13] Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive Surgery Combined with Perioperative Intraperitoneal Chemotherapy for the Management of Peritoneal Carcinomatosis from Colorectal Cancer: A Multi-Institutional Study. J Clin Oncol 2004;22:3284–92. https://doi.org/10.1200/JCO.2004.10.012.

[14] Quénet F, Elias D, Roca L, Goéré D, Ghouti L, Pocard M, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:256–66. https://doi.org/10.1016/S1470-2045(20)30599-4.