

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.ejcancer.com](http://www.ejcancer.com)

Original Research

# UGT1A1 genotype-guided dosing of irinotecan: A prospective safety and cost analysis in poor metaboliser patients



Emma C. Hulshof<sup>a,b</sup>, Mirjam de With<sup>c,d</sup>, Femke M. de Man<sup>c</sup>,  
Geert-Jan Creemers<sup>e</sup>, Birgit A.L.M. Deiman<sup>f</sup>, Jesse J. Swen<sup>b</sup>,  
Saskia Houterman<sup>g</sup>, Stijn L.W. Koolen<sup>c,h</sup>, Sander Bins<sup>c</sup>,  
Anna M.J. Thijs<sup>e</sup>, Marjan M.J. Laven<sup>e</sup>, Anke M. Hövels<sup>i</sup>,  
Saskia A.C. Luelmo<sup>j</sup>, Danny Houtsma<sup>k</sup>, Katerina Shulman<sup>l</sup>,  
Howard L. McLeod<sup>m</sup>, Ron H.N. van Schaik<sup>d</sup>, Henk-Jan Guchelaar<sup>b</sup>,  
Ron H.J. Mathijssen<sup>c</sup>, Hans Gelderblom<sup>j</sup>, Maarten J. Deenen<sup>a,b,\*</sup>

<sup>a</sup> Department of Clinical Pharmacy, Catharina Hospital, Eindhoven, the Netherlands

<sup>b</sup> Department of Clinical Pharmacy and Toxicology, Leiden University Medical Centre, Leiden, the Netherlands

<sup>c</sup> Department of Medical Oncology, Erasmus University Medical Centre, Rotterdam, the Netherlands

<sup>d</sup> Department of Clinical Chemistry, Erasmus University Medical Centre, Rotterdam, the Netherlands

<sup>e</sup> Department of Medical Oncology, Catharina Hospital, Eindhoven, the Netherlands

<sup>f</sup> Department of Molecular Biology, Catharina Hospital, Eindhoven, the Netherlands

<sup>g</sup> Department of Education and Research, Catharina Hospital, Eindhoven, the Netherlands

<sup>h</sup> Department of Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam, the Netherlands

<sup>i</sup> Hövels Consultancy HTA and Health Economics, Bilthoven, the Netherlands

<sup>j</sup> Department of Medical Oncology, Leiden University Medical Centre, Leiden, the Netherlands

<sup>k</sup> Department of Medical Oncology, Haga Hospital, The Hague, the Netherlands

<sup>l</sup> Department of Medical Oncology, Carmel Medical Centre and Clalit Haifa District Regional Oncology Clinics, Haifa, Israel

<sup>m</sup> University of South Florida Taneja College of Pharmacy, Tampa, FL, USA

Received 5 August 2021; received in revised form 25 November 2021; accepted 5 December 2021

Available online 5 January 2022

## KEYWORDS

UDP-glucuronosyl  
transferase;  
UGT;  
Pharmacogenetics;

**Abstract** *Aim:* To determine the safety, feasibility, pharmacokinetics, and cost of *UGT1A1* genotype-guided dosing of irinotecan.

*Patients and methods:* In this prospective, multicentre, non-randomised study, patients intended for treatment with irinotecan were pre-therapeutically genotyped for *UGT1A1*\*28 and *UGT1A1*\*93. Homozygous variant carriers (*UGT1A1* poor metabolisers; PMs) received

\* Corresponding author: Department of Clinical Pharmacy, Catharina Hospital, Michelangelolaan 2, Eindhoven, 5623 EJ, the Netherlands.  
E-mail address: [maarten.deenen@catharinaziekenhuis.nl](mailto:maarten.deenen@catharinaziekenhuis.nl) (M.J. Deenen).

<https://doi.org/10.1016/j.ejca.2021.12.009>

0959-8049/© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Irinotecan;  
Genotyping;  
Toxicity

an initial 30% dose reduction. The primary endpoint was incidence of febrile neutropenia in the first two cycles of treatment. Toxicity in UGT1A1 PMs was compared to a historical cohort of UGT1A1 PMs treated with full dose therapy, and to UGT1A1 non-PMs treated with full dose therapy in the current study. Secondary endpoints were pharmacokinetics, feasibility, and costs.

**Results:** 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.

**Conclusion:** *UGT1A1* genotype-guided dosing significantly reduces the incidence of febrile neutropenia in UGT1A1 PM patients treated with irinotecan, results in a therapeutically effective systemic drug exposure, and is cost-saving. Therefore, *UGT1A1* genotype-guided dosing of irinotecan should be considered standard of care in order to improve individual patient safety.

© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Irinotecan is a commonly prescribed anticancer drug for the treatment of advanced colorectal and pancreatic cancer. However, treatment with irinotecan is often complicated by severe adverse events (AEs) such as febrile neutropenia and diarrhea [1]. This may lead to hospitalisation, loss of quality of life, treatment delay, and even treatment discontinuation. Irinotecan is a prodrug that is activated via carboxylesterases in the liver and blood to SN-38 [1]. SN-38 in turn is inactivated in the liver and intestines into SN-38-glucuronide by UDP-glucuronosyltransferase 1A1 (UGT1A1). UGT1A1 is the main enzyme responsible for the inactivation of SN-38 [2].

Several genetic variants within the *UGT1A1* gene are known to be associated with a higher exposure to SN-38 and, therefore, with an increased risk for irinotecan-associated severe AEs [3]. Two highly prevalent and clinically relevant genetic variants in *UGT1A1* in the Caucasian population are *UGT1A1*\*28 and *UGT1A1*\*93 [4,5]. *UGT1A1*\*28 is a tandem repeat polymorphism in the promoter region of the *UGT1A1* gene that leads to reduced enzyme activity [6,7]. Homozygous carriers of this variant have a decreased *UGT1A1* gene expression of up to 70% and are considered UGT1A1 poor metabolisers (UGT1A1 PM) [7]. *UGT1A1*\*93 is in partial linkage disequilibrium (LD) with *UGT1A1*\*28 ( $r^2 = 0.83$ ; <https://ldlink.nci.nih.gov/>).

A considerable amount of case reports and genetic association studies has been published on the increased risk for irinotecan-associated AEs in homozygous *UGT1A1*\*28 variant allele carriers [8–13]. Moreover, multiple meta-analyses have confirmed this association [14–18]. Besides the *UGT1A1*\*28 polymorphism, a replication

study confirmed that *UGT1A1*\*93 is also strongly associated with an increased risk of irinotecan-induced neutropenia [4].

Despite these compelling results, prospective clinical studies have still not been conducted and *UGT1A1* genotyping is not being routinely applied. The main reason for this is that no alternative dose is available for UGT1A1 PM patients. We hypothesised that *UGT1A1* genotype-guided dosing of irinotecan reduces the risk of severe AEs, and thereby improves the individual patient safety. Therefore, to the best of our knowledge, for the first time the safety, feasibility, pharmacokinetics, and costs of *UGT1A1* genotype-guided dosing of irinotecan was studied in UGT1A1 PM patients.

## 2. Methods

### 2.1. Study design

This was a prospective, multicentre, nonrandomised clinical implementation study conducted in two large teaching hospitals and two academic centres in the Netherlands. The primary endpoint was febrile neutropenia during the first two cycles of treatment with irinotecan. Secondary endpoints were: other toxicities, treatment delay due to *UGT1A1* genotyping (feasibility), pharmacokinetics of irinotecan and SN-38 in UGT1A1 PMs, cost of *UGT1A1* genotype-guided dosing of irinotecan, conjugated bilirubin, and total bilirubin plasma concentrations.

Toxicity in UGT1A1 PMs was compared to historical control patients, i.e. patients homozygous polymorphic for *UGT1A1*\*28 and/or *UGT1A1*\*93 treated with full dose therapy identified from systematic literature search. In addition, toxicity in UGT1A1 PMs was compared to

UGT1A1 non-PMs treated with full dose in the current study, under the assumption that these groups would experience comparable degrees of toxicity. The study was approved by a central medical ethical review board, the Medical Research Ethics Committees United, and approval from the board of directors of each individual hospital was obtained for all participating centres. The study was registered at the Netherlands Trial Register ([www.trialregister.nl](http://www.trialregister.nl) study-number NL6270).

## 2.2. Patient selection

Patients were included if they were aged 18 years or older with a pathologically confirmed malignancy intended to be treated with irinotecan at a dose of  $\geq 180$  mg/m<sup>2</sup> or 450–600 mg flat dose. For further inclusion and exclusion criteria see [Supplementary Methods](#).

Historical controls were selected from published studies identified from a systematic literature search in which unselected cohorts of irinotecan-treated Caucasian patients with pancreatic or colorectal cancer were genotyped for *UGT1A1*\*28. Further selection criteria are described in the [Supplementary Methods](#).

## 2.3. Procedures

Prior to start of treatment with irinotecan, patients were genotyped for *UGT1A1*\*28 and *UGT1A1*\*93. Genotypes were converted to phenotypes in the following manner: homozygous carriers of *UGT1A1*\*28 and/or *UGT1A1*\*93 were defined UGT1A1 PM, heterozygous carriers of *UGT1A1*\*28 and/or *UGT1A1*\*93 were defined UGT1A1 intermediate metaboliser (UGT1A1 IM) and *UGT1A1* wild type individuals were defined UGT1A1 extensive metaboliser, i.e. normal metaboliser (UGT1A1 EM).

UGT1A1 PMs were given an initial irinotecan dose reduction of 30% in cycle 1 based on previous pharmacokinetic and clinical evidence [19–22]. Thereafter, the dose was further individualized based on ANC and clinical tolerance. [Supplementary Figs. S1 and S2](#) depict the dosing nomogram for UGT1A1 PMs.

Toxicity was graded according to NCI CTCAE version 4.03 [23].

In order to determine adequate drug exposure of reduced dosing in UGT1A1 PMs the pharmacokinetics of irinotecan and SN-38 was determined by use of a limited sampling strategy ([Supplementary Methods](#)) [24]. Both irinotecan and SN-38 concentrations at 2.5 h and 49.5 h as well as systemic SN-38 exposure (area under the concentration–time curve, AUC<sub>0–500h</sub>) of reduced dosing in the UGT1A1 PM cohort were analysed and compared to a standard dosed irinotecan patient cohort [25]. Given the various irinotecan treatment schedules included in the study all irinotecan and SN-38 concentrations and SN-38 AUCs were dose-normalised for UGT1A1 PM to 126 mg/m<sup>2</sup> (corresponding to 70% dose intensity) and for

the standard dosed cohort to 180 mg/m<sup>2</sup> (100% dose intensity).

A cost analysis was conducted from a health care perspective. Direct health care costs were calculated, based on costs of screening and subsequent drug treatment and treatment for toxicity. The impact of parameter uncertainty on model outcomes was analysed using one-way sensitivity analyses in which each of the parameters were individually varied by  $\pm 20\%$ . Further details are provided in the [Supplementary Methods](#).

## 2.4. Statistical analysis

Based on prior data we assumed that the intervention reduces the incidence of febrile neutropenia from 26% to 3%, similar to the incidence of febrile neutropenia in wild type and heterozygous carriers [26–28]. Based on this assumption, a total of 31 UGT1A1 PMs and 47 historical control were needed to demonstrate the abovementioned reduction in incidence of febrile neutropenia with a power of 80% and a 2-sided test with an alpha of 0.05.

Patients were considered evaluable if they received at least one dose of irinotecan. Treatment outcomes were analysed using the Chi-square test or Fisher's exact test, where applicable. Pharmacokinetic data was presented as geometric mean and the coefficient of variation. The relative difference between UGT1A1 PMs and the standard dosed cohort was calculated and was analysed using an unpaired t-test. All statistical tests were 2-sided and were performed using a 5% significance level. All statistical analyses were performed with SPSS for Windows (version 25.0; IBM Corp., Armonk, NY).

Additional details of the study methods and results, including subgroup analysis, genotype frequencies, and bilirubin plasma concentrations, are provided in the [Supplementary Methods](#) and [Supplementary Results](#).

## 3. Results

Between August 2017 and December 2020, a total of 404 consecutive patients were pre-therapeutically genotyped for the selected *UGT1A1* polymorphisms and enrolled in this study. In total, 54 patients were excluded either because of screen failures, refrain from chemotherapy or loss to follow-up ([Fig. 1](#)).

### 3.1. Overall patient and treatment characteristics

Of the 350 evaluable patients, a total of 8.9% ( $N = 31$ ) was UGT1A1 PM, individual genotype frequencies are reported in [Supplementary Table S1](#). [Table 1](#) presents an overview of the baseline characteristics of all patients. Given the heterogeneous patient population with regard to line of treatment, we tested whether the incidences of febrile neutropenia and neutropenia grade  $\geq 3$  differed between pre-treated and first-line treatment patients;

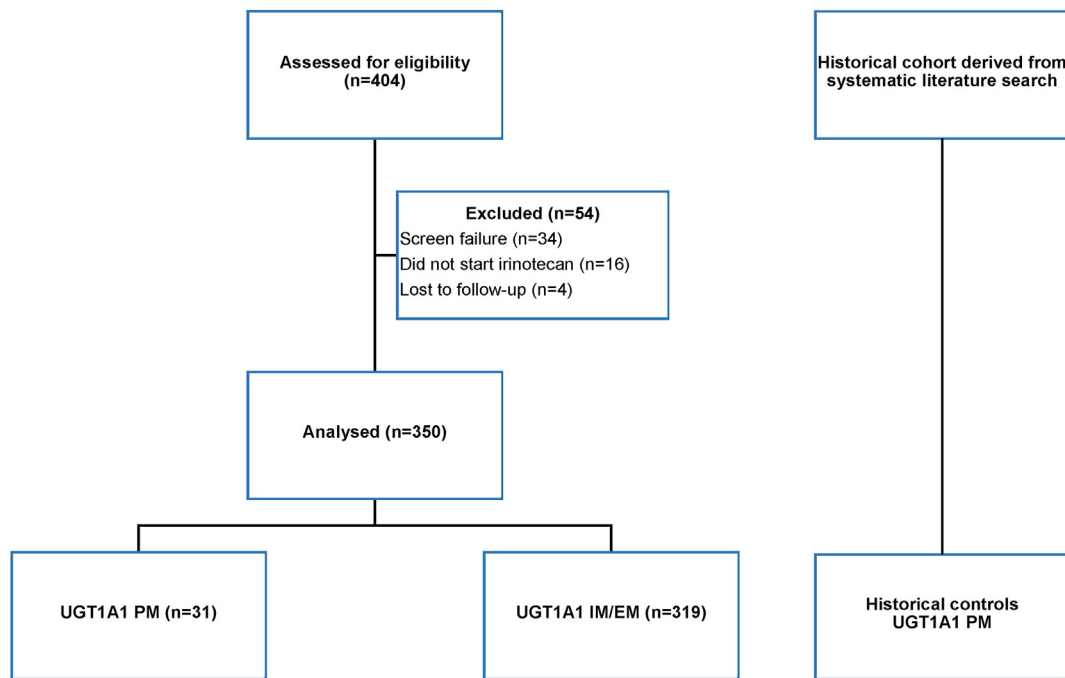


Fig. 1. Consort diagram of the study. *Abbreviations:* UGT1A1 PM = UGT1A1 poor metaboliser; UGT1A1 IM = UGT1A1 intermediate metaboliser; UGT1A1 EM = UGT1A1 extensive metaboliser.

however, this was not the case (data not shown). UGT1A1 PMs were treated with a median dose intensity of irinotecan in the first cycle of 70% (IQR 67.8%–70.6%) compared to 99% (IQR 97%–101%) in UGT1A1 non-PMs. The overall median dose intensity was 69% (IQR: 60%–71%) versus 96% (IQR: 81%–100%), respectively. Furthermore, pre-therapeutic genotyping showed to be feasible: in only one (0.3%) of all 350 evaluable patients genotype results were delayed and treatment with irinotecan was initiated before genotyping results were available.

### 3.2. Toxicity of UGT1A1 genotype-guided dosing

Systematic literature research revealed a total of nine studies that fulfilled the selection criteria for the historical cohort (Supplementary Table S2) [8,16,26–32]. In this study, the incidence of febrile neutropenia in the first two cycles in UGT1A1 PMs treated with UGT1A1 genotype-guided dosing was 7% and was significantly lower compared to 24% in historical controls treated with full dose therapy ( $P = .04$ ; Fig. 2). Besides the primary endpoint, the incidence of grade  $\geq 4$  neutropenia (13% versus 56%;  $P < .01$ ) and chemotherapy-related hospital admissions (13% versus 42%;  $P < .01$ ) was also significantly lower in UGT1A1 PMs than in historical controls. The incidence of grade  $\geq 3$  diarrhea was also reduced, but not statistically significant (10% versus 22%;  $P = .14$ ).

In comparison to UGT1A1 IM/EMs treated with full dose therapy in this study, the incidence of febrile

neutropenia of genotype-guided dosing in UGT1A1 PMs was in line with the hypothesis and comparable with the incidence of 4.1% in UGT1A1 non-PMs treated with full dose therapy ( $P = .63$ ; Fig. 2). Despite initial 30% dose reduction, UGT1A1 PMs experienced more grade  $\geq 3$  neutropenia (39% versus 17%;  $P < .01$ ) and overall grade  $\geq 3$  toxicity (58% versus 35%;  $P = .01$ ). An overview of all toxicity outcomes of UGT1A1 genotype-guided dosing is presented in Table 2.

In subgroup analysis, the incidence of grade  $\geq 3$  neutropenia (22% versus 11%;  $P < .01$ ) and grade  $\geq 4$  neutropenia (12% versus 6%;  $P = .04$ ) was higher in UGT1A1 IMs compared to UGT1A1 EMs, respectively. Supplementary Table S3 lists all results of the subgroup analyses.

### 3.3. Pharmacokinetics

The initial 30% dose reduction in UGT1A1 PMs was reflected in significantly lower ( $-30\%$ ,  $P < .01$ ) mean irinotecan plasma concentration compared to the standard dosed control cohort. Of interest, whilst applying the 30% dose reduction, the systemic exposure of the active metabolite SN-38 of reduced dosing in UGT1A1 PMs ( $N = 17$ ) was slightly higher compared to the standard dosed irinotecan patient cohort ( $N = 46$ ) with a borderline significant relative difference in SN-38  $AUC_{0-500h}$  of +32% (95% CI:  $-0.5\%$ –75.8%) and a geometric mean (CV) of 391 ng\*h/mL (43.7%) versus 296 ng\*h/mL (75.3%), respectively. All pharmacokinetic data are provided in Fig. 3 and Table 3.

Table 1  
Baseline characteristics.

	UGT1A1 PM N = 31	UGT1A1 IM N = 158	UGT1A1 EM N = 161	All patients N = 350
Sex, No. (%)				
Male	19 (61)	89 (56)	81 (50)	189 (54)
Female	12 (39)	69 (44)	80 (50)	161 (46)
Age, median (IQR), years	61 (58–67)	63 (57–69)	63 (56–71)	63 (57–69)
Ethnic origin, No. (%)				
Caucasian	29 (94)	155 (98)	159 (98)	343 (98)
African descent	2 (6)	2 (1)	1 (1)	5 (1)
Hispanic	0 (0.0)	1 (1)	1 (1)	2 (1)
Cancer type, No. (%)				
Pancreatic cancer	14 (45)	82 (52)	78 (48)	174 (50)
Colorectal cancer	13 (42)	63 (40)	74 (46)	150 (43)
Other <sup>a</sup>	4 (13)	13 (8)	9 (6)	26 (7)
Cancer stage, No. (%)				
Local	1 (3)	17 (11)	16 (10)	34 (10)
Locally advanced	10 (32)	32 (20)	41 (25)	83 (24)
Metastatic	20 (65)	109 (69)	104 (65)	233 (66)
Previous treatment with chemotherapy <sup>b</sup> , No. (%)	16 (52)	81 (51)	88 (55)	185 (53)
Treatment regimen, No. (%)				
FOLFIRINOX q2w <sup>c</sup>	14 (45)	79 (50)	80 (50)	173 (50)
FOLFIRI q2w <sup>c</sup>	5 (16)	32 (20)	27 (17)	64 (18)
FOLFIRI q2w + targeted agent <sup>c</sup>	3 (9)	12 (8)	17 (11)	32 (9)
Irinotecan q3w <sup>d</sup>	7 (23)	18 (11)	19 (11)	44 (13)
Other	2 (7)	17 (11)	18 (11)	37 (11)
WHO performance status, No. (%)				
0	6 (19)	37 (23)	40 (25)	83 (24)
1	13 (42)	54 (34)	58 (36)	125 (36)
2	1 (3)	3 (2)	3 (2)	7 (2)
0–2; not specified <sup>e</sup>	11 (36)	64 (41)	60 (37)	135 (38)
BSA, median (IQR), m <sup>2</sup>	1.80 (1.70–2.01)	1.93 (1.79–2.06)	1.89 (1.74–2.04)	1.90 (1.75–2.04)

Abbreviations: UGT1A1 PM = UGT1A1 poor metaboliser; UGT1A1 IM = UGT1A1 intermediate metaboliser; UGT1A1 EM = UGT1A1 extensive metaboliser.

<sup>a</sup> Cancer type: esophagus ( $n = 9$ ), biliary tract ( $n = 4$ ), gastric ( $n = 4$ ), unknown origin ( $n = 3$ ), duodenum ( $n = 2$ ), liposarcoma ( $n = 1$ ), lung ( $n = 1$ ), neuroendocrine sigmoid ( $n = 1$ ), urothelial ( $n = 1$ ).

<sup>b</sup> Chemotherapy not containing irinotecan, previous irinotecan treatment was an exclusion criterion.

<sup>c</sup> Irinotecan dose 180 mg/m<sup>2</sup>.

<sup>d</sup> Irinotecan flat dose 600 mg.

<sup>e</sup> WHO performance status (WHO PS) not further specified. However, WHO PS was always 0–2 as it was properly evaluated as inclusion criterion.

### 3.4. Cost analysis

Supplementary Fig. S3 and Supplementary Table S4 provide the decision tree and the parameter estimates used in the cost analysis, respectively. The expected total treatment costs of *UGT1A1* genotype-guided dosing were €7232 per patient compared to €7415 per patient for conventional dosing. Thereby, genotype-guided dosing resulted in a total cost reduction of €183 per patient, outweighing screening costs (Supplementary Table S5). The tornado diagram (Fig. 4) shows the effect on the cost reduction of *UGT1A1* genotyping when all model parameters were individually varied by 20%. The model proved to be most sensitive to UGT1A1 PM frequency.

## 4. Discussion

This is the first prospective clinical study providing evidence of *UGT1A1* genotype-guided dosing of

irinotecan in all UGT1A1 phenotypes. We demonstrated that genotype-guided dosing significantly reduced the incidence of febrile neutropenia and chemotherapy-related hospital admissions in UGT1A1 PMs. Nonetheless, systemic drug exposure of the active metabolite SN-38 remained adequate and was even slightly higher. This shows 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.

*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. Three previously published cost analyses suggested *UGT1A1* genotype-guided dosing resulted in cost reductions ranging from €112 up to €596 per patient, however, this was calculated retrospectively [33–35]. In this cost

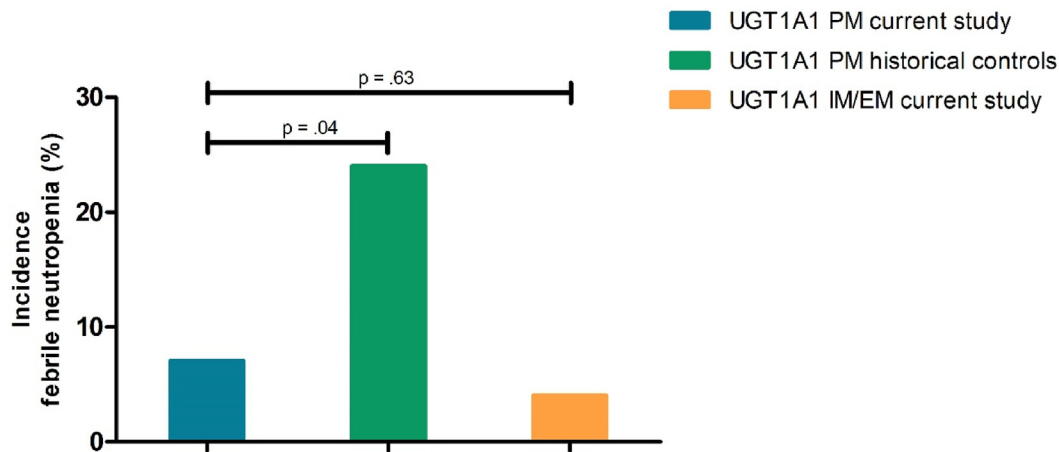


Fig. 2. Incidence of febrile neutropenia. The incidence (%) of febrile neutropenia in the first two cycles in; UGT1A1 PMs included in this study and treated with *UGT1A1* genotype-guided dosing, UGT1A1 PM historical controls treated with the full dose therapy, and UGT1A1 IM/EMs (non-PMs) treated with fill dose therapy in this study. Abbreviations: UGT1A1 PM = UGT1A1 poor metabolisers, UGT1A1 IM/EM = UGT1A1 intermediate and extensive metabolisers.

study, conducted alongside the clinical trial, we confirm a total saving of €183 per patient.

The overall dose intensity in UGT1A1 PMs was 69% (IQR 60%–70%), which confirms the previously reported maximum tolerated dose intensities in three dose-finding studies. These studies reported dose intensities

ranging from 43% to 72%, indicating that a 30% dose reduction in UGT1A1 PMs is adequate [20,21,36]. In addition, a French proof of concept trial demonstrated that *UGT1A1* genotype-guided dosing of FOLFIRI with irinotecan dose intensification based on tolerance, resulted in a mean irinotecan dose in UGT1A1 PMs

Table 2  
Treatment outcomes for patients included in this study and historical controls.

	UGT1A1 PM current study		UGT1A1 PM historical controls			UGT1A1 IM/EM current study	
	(N = 31)	(N)	(N)	Reference <sup>a</sup>	P value	(N = 319)	P value
Dose intensity 1 <sup>st</sup> cycle, median (IQR)	70.0% (67.8–70.6%)	100% <sup>b</sup>	n.a.	n.a.	n.a.	99.4% (97.2–100.6%)	n.a.
Dose intensity all cycles, median (IQR)	69.4% (60.0–71.2%)	unknown	n.a.	n.a.	n.a.	95.6% (81.0–100.0%)	n.a.
Hematologic toxicity, No. (%)							
Febrile neutropenia in the first two cycles	2 (7)	12 (24) <sup>c</sup>	50	[26–28]	.04	13 (4)	.63
Febrile neutropenia	3 (10)	12 (24)	50	[26–28]	.11	15 (5)	.21
Grade ≥3 neutropenia	12 (39)	43 (35)	122	[16]	.72	53 (17)	< .01
Grade ≥4 neutropenia	4 (13)	14 (56)	25	[8,27,29]	< .01	28 (13)	.51
Grade ≥3 leukopenia	5 (16)	8 (32)	25	[26]	.16	38 (12)	.56
Grade ≥3 thrombocytopenia	0 (0.0)	unknown	n.a.	n.a.	n.a.	4 (1)	1.00
Non-hematologic toxicity, No. (%)							
Grade ≥3 diarrhea	3 (10)	25 (22)	116	[16]	.14	51 (16)	.44
Grade ≥3 nausea	1 (3)	unknown	n.a.	n.a.	n.a.	18 (6)	1.00
Grade ≥3 anorexia	2 (7)	unknown	n.a.	n.a.	n.a.	12 (4)	.36
Grade ≥3 other toxicity	4 (13)	unknown	n.a.	n.a.	n.a.	34 (11)	.76
Overall grade ≥3 toxicity	18 (58)	39 (52)	75	[28,30,31]	.57	112 (35)	.01
Chemotherapy-related hospital admissions <sup>d</sup> , No. (%)	4 (13)	22 (42)	53	[8,26,32]	< .01	72 (23)	.21
Early treatment withdrawal due to toxicity, No. (%)	3 (10)	unknown	n.a.	n.a.	n.a.	32 (10)	1.00
Treatment delay due to toxicity, No. (%)	12 (39)	unknown	n.a.	n.a.	n.a.	85 (27)	.15

Abbreviations: UGT1A1 PM = UGT1A1 poor metabolisers; UGT1A1 IM/EM = UGT1A1 intermediate and extensive metabolisers; n.a. = not applicable.

<sup>a</sup> Historical controls were selected per treatment outcome, therefore different publications per outcome are reported.

<sup>b</sup> Dose intensity in cycle 1 was not always reported, based on the inclusion criteria for the historical cohort it was assumed that no dose reductions were performed since the intention was to treat patients with full dose.

<sup>c</sup> From 2 historical control cohorts (N = 36) the incidence of febrile neutropenia was only available for all cycles [26,27].

<sup>d</sup> Hospital admissions due to toxicity of irinotecan alone, or due to toxicity of combination of chemotherapy.

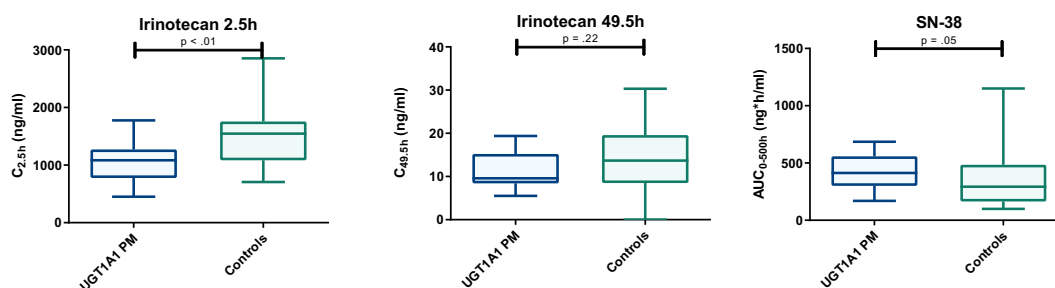


Fig. 3. Plasma concentrations of irinotecan and AUCs of its active metabolite SN-38 of reduced dosing in UGT1A1 PMs versus standard dosed irinotecan patient cohort. All irinotecan plasma concentrations and SN-38 AUCs were dose-normalised for UGT1A1 PM to 126 mg/m<sup>2</sup> (corresponding with 70% dose intensity) and for the standard dosed cohort to 180 mg/m<sup>2</sup> (100% dose intensity) to correct for the various irinotecan treatment regimens included in this study. Abbreviations: C = concentration; UGT1A1 PM = UGT1A1 poor metaboliser; AUC = area under the curve.

after three months of 140 mg/m<sup>2</sup> (dose intensity 78%) [37]. Our pharmacokinetic analysis shows a slightly higher exposure to SN-38 in UGT1A1 PMs of reduced dosing versus controls. Notwithstanding, incidences of grade 4 neutropenia, febrile neutropenia and diarrhea in UGT1A1 PMs was comparable to the incidences in UGT1A1 non-PMs. In addition, the overall median dose intensity was 69%, demonstrating good tolerance over time. Therefore, a starting dose reduction of 30% in UGT1A1 PMs is sufficient, and should not necessarily be further reduced despite slightly higher SN-38 systemic exposure.

Hereby, we believe this study adds important data. Similarly to pre-therapeutic genotyping of dihydropyrimidine dehydrogenase (DPD; *DPYD*) in patients treated with capecitabine or 5-fluorouracil, it must be noted that the same efforts were carried out before *DPYD* genotyping in fluoropyrimidine treatment was accepted and implemented by most cancer societies.

There are some potential drawbacks associated with our study. First, the ideal study design would have been a randomised controlled trial with a *UGT1A1* genotype-

guided dosing arm and a conventional dosing arm that is also powered to assess survival outcomes. However, such a trial is hardly feasible, since at least 6000 patients need to be prospectively screened for inclusion. More important, with the available evidence favoring genotype-guided dosing and the known risk of overexposure with standard dosing, it is rather unethical to randomise patients. Nonetheless, the 30% dose reduction of irinotecan in UGT1A1 PMs resulted in a slightly higher systemic exposure to SN-38 as in a standard dosed patient cohort. Therefore, we consider it unlikely that *UGT1A1* genotype-guided dosing will negatively affect overall survival.

Second, patients and historical controls on different treatment schedules of irinotecan, with different cancer types and different lines of therapy were included in this study. Nevertheless, by dose normalisation of the pharmacokinetic data, and by reporting only adverse events related to irinotecan treatment, the different treatment schedules did not affect study results. In addition, previous treatment with chemotherapy was not related to the incidence of febrile neutropenia nor grade  $\geq 3$  neutropenia in this cohort.

Table 3

Pharmacokinetics of irinotecan and its active metabolite SN-38 in UGT1A1 PMs versus standard dosed irinotecan patient cohort.

PK parameters	UGT1A1 PM (Geometric mean, CV)	n <sup>a</sup>	Standard dosed cohort (Geometric mean, CV)	n <sup>a</sup>	Relative difference UGT1A1 PM vs. standard dosed cohort (95% CI)	P value
Plasma irinotecan <sup>b</sup>						
C <sub>2.5h</sub> , ng/mL	999 (34.3%)	17	1419 (32.7%)	45	-29.6% (-41.4% to -15.4%)	< .01
C <sub>49.5h</sub> , ng/mL	10.7 (37.1%)	17	12.8 (60.7%)	44	-16.5% (-37.7%–12.0%)	.22
Plasma SN-38 <sup>b</sup>						
C <sub>2.5h</sub> , ng/mL	18.3 (47.3%)	17	20.0 (60.4%)	46	-8.3% (-32.2%–24.0%)	.57
C <sub>49.5h</sub> , ng/mL	1.65 (61.0%)	17	0.89 (123.5%)	46	+84.8% (24.4%–174.5%)	< .01
AUC <sub>0-500h</sub> , ng*h/mL	391 (43.7%)	17	296 (75.3%)	46	+32.2% (-0.50%–75.8%)	.05

Pharmacokinetic data of UGT1A1 PMs with a reduced dose of irinotecan and a control cohort with a standard dose of irinotecan.

Abbreviations: UGT1A1 PM = UGT1A1 poor metaboliser; CV = coefficient of variation; CI = confidence interval.

<sup>a</sup> Not all UGT1A1 PMs (14/31) participated in the PK part of the study because not all patients consented or due to logistic reasons blood sampling was not possible.

<sup>b</sup> All data are dose-normalised for UGT1A1 PM to 126 mg/m<sup>2</sup> (corresponding with 70% dose intensity) and for the standard dosed cohort to 180 mg/m<sup>2</sup> to be able to compare all different dosing levels in this study.

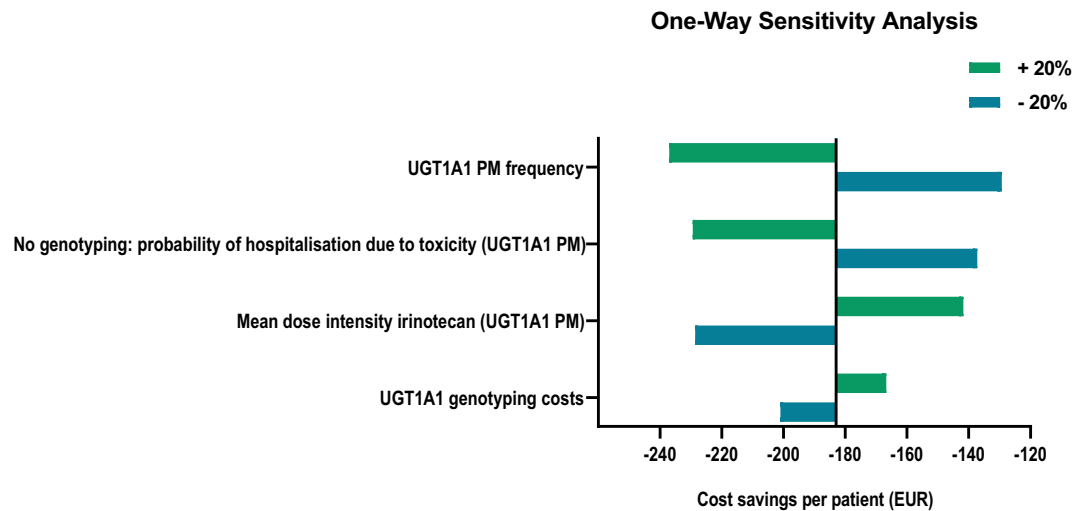


Fig. 4. One-way sensitivity analysis of UGT1A1 genotype-guided dosing of irinotecan versus conventional dosing of irinotecan. Abbreviations: UGT1A1 PM = UGT1A1 poor metaboliser.

Third, while G-CSF use was allowed in this study, this information could not be retrieved for most of the historical controls. G-CSF use might influence the risk of febrile neutropenia. Nonetheless, the incidence of febrile neutropenia in our UGT1A1 PMs was comparable with the incidence in our UGT1A1 non-PMs treated with full dose therapy. Moreover, in comparison to UGT1A1 non-PMs treated with full dose therapy in this study, UGT1A1 PMs experienced more grade  $\geq 3$  neutropenia (39% versus 17%) indicating that neutropenia still occurred in our study despite allowance of G-CSF use.

Based on the lower incidence of grade  $\geq 3$  neutropenia in UGT1A1 EMs compared to UGT1A1 IMs in our subgroup analysis and on several dose-finding studies of irinotecan in UGT1A1 IM and EM patients, further research into optimising the safety of irinotecan treatment in UGT1A1 IM patients is of great interest [38,39]. It should be noted that the results of our study are not directly applicable for the Asian population, but could potentially be extrapolated. However, since in Asian patients the *UGT1A1\*6* rather than *UGT1A1\*28* is of major importance, Asians were excluded in our study [40].

## 5. Conclusion

In conclusion, the results of this prospective study show that *UGT1A1* genotype-guided dosing significantly reduces the incidence of febrile neutropenia in UGT1A1 PM patients treated with irinotecan, is feasible in daily practice and is cost-saving. In addition, systemic drug exposure of the active metabolite remained at least adequate with applying a 30% dose reduction. Therefore, *UGT1A1* genotype-guided dosing of irinotecan should be considered new standard of care in order to improve the individual patient safety.

## Author contributions

**Emma C Hulshof:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Resources, Writing – original draft, Writing – review & editing, Project administration. **Mirjam de With:** Validation, Formal analysis, Investigation, Data curation, Resources, Writing – original draft, Writing – review & editing, Project administration. **Femke M de Man:** Conceptualization, Methodology, Investigation, Data curation, Resources, Project administration, Writing – review & editing. **Geert-Jan Creemers:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing. **Birgit ALM Deiman:** Investigation, Resources, Writing – review & editing. **Jesse J Swen:** Conceptualization, Methodology, Resources, Writing – review & editing. **Saskia Houterman:** Formal analysis, Data curation, Resources, Writing – review & editing. **Stijn LW Koolen:** Investigation, Resources, Writing – review & editing. **Sander Bins:** Resources, Writing – review & editing. **Anna MJ Thijs:** Resources, Writing – review & editing. **Marjan MJ Laven:** Conceptualization, Methodology, Data curation, Resources, Writing – review & editing. **Anke M Hövels:** Formal analysis, Investigation, Writing – review & editing. **Saskia AC Luelmo:** Data curation, Resources, Writing – review & editing. **Danny Houtsma:** Data curation, Resources, Writing – review & editing. **Katerina Shulman:** Data curation, Resources, Writing – review & editing. **Howard L McLeod:** Data curation, Resources, Writing – review & editing. **Ron HN van Schaik:** Investigation, Resources, Writing – review & editing. **Henk-Jan Guchelaar:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing. **Ron HJ Mathijssen:** Conceptualization, Methodology, Investigation, Resources, Writing –



review & editing. **Hans Gelderblom**: Conceptualization, Methodology, Investigation, Resources, Writing – review & editing. **Maarten J Deenen**: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Resources, Writing – original draft, Writing – review & editing, Project administration.

### Funding/Support

This study was sponsored by the Catharina Research Foundation, Eindhoven, the Netherlands. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. ECH and MJD had full access to all the data in the study, and MJD had final responsibility for the decision to submit for publication.

### Data sharing statement

The study protocol and statistical analysis plan are included with the submission of the manuscript. De-identified individual patient may be provided at reasonable request to researchers who provide a methodologically sound proposal for the purpose of e.g. individual participant data meta-analysis. Proposals should be directed to the corresponding author at [maarten.deenen@catharinaziekenhuis.nl](mailto:maarten.deenen@catharinaziekenhuis.nl).

### Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: HLMcL declares the following potential conflicts of interest: Board of Directors: Vyant Bio; Co-Founder: Clariifi LLC; Advisor: EviCore, Total Dx Connect, and Viecure.

All remaining authors declare no potential conflicts of interest.

### Acknowledgments

All four participating centres are acknowledged for their contribution to patient inclusion.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2021.12.009>.

### References

- [1] 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>.
- [2] Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther* 2012;92:414–7. <https://doi.org/10.1038/clpt.2012.96>.
- [3] Mathijssen RHJ, Gurney H. Irinogenetics: how many stars are there in the sky? *J Clin Oncol* 2009;27:2578–9. <https://doi.org/10.1200/JCO.2008.21.2480>.
- [4] Crona DJ, Ramirez J, Qiao W, De Graan AJ, Ratain MJ, Van Schaik RHN, et al. Clinical validity of new genetic biomarkers of irinotecan neutropenia: an independent replication study. *Pharmacogenomics J* 2016;16:54–9. <https://doi.org/10.1038/tpj.2015.23>.
- [5] Innocenti F, Kroetz DL, Schuetz E, Dolan ME, Ramirez J, Relling M, et al. Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics. *J Clin Oncol* 2009;27:2604–14. <https://doi.org/10.1200/JCO.2008.20.6300>.
- [6] Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci U S A* 1998;95:8170–4. <https://doi.org/10.1073/pnas.95.14.8170>.
- [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/nejm.199511023331802>.
- [8] Rouits E, Boisdrion-Celle M, Dumont A, Guérin O, Morel A, Gamelin E. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients. *Clin Cancer Res* 2004;10:5151–9. <https://doi.org/10.1158/1078-0432.CCR-03-0548>.
- [9] Satoh T, Ura T, Yamada Y, Yamazaki K, Tsujinaka T, Munakata M, et al. Genotype-directed, dose-finding study of irinotecan in cancer patients with UGT1A1\*28 and/or UGT1A1\*6 polymorphisms. *Cancer Sci* 2011;102:1868–73. <https://doi.org/10.1111/j.1349-7006.2011.02030.x>.
- [10] Jannin A, Hennart B, Adenis A, Chauffert B, Penel N. Life-threatening irinotecan-induced toxicity in an adult patient with alveolar rhabdomyosarcoma: the role of a UGT1A1 polymorphism. *Case Rep Oncol Med* 2017;2017:1–3. <https://doi.org/10.1155/2017/2683478>.
- [11] Marcuello E, Altés A, Menoyo A, Del Rio E, Gómez-Pardo M, Baiget M. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. *Br J Cancer* 2004;91:678–82. <https://doi.org/10.1038/sj.bjc.6602042>.
- [12] Massacesi C, Terrazzino S, Marcucci F, Rocchi MB, Lippe P, Bissoni R, et al. Uridine diphosphate glucuronosyl transferase 1A1 promoter polymorphism predicts the risk of gastrointestinal toxicity and fatigue induced by irinotecan-based chemotherapy. *Cancer* 2006;106:1007–16. <https://doi.org/10.1002/cncr.21722>.
- [13] Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004;22:1382–8. <https://doi.org/10.1200/JCO.2004.07.173>.
- [14] Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. UGT1A1\*28 genotype and irinotecan-induced neutropenia: dose matters. *J Natl Cancer Inst* 2007;99:1290–5. <https://doi.org/10.1093/jnci/djm115>.
- [15] Hu ZY, Yu Q, Pei Q, Guo C. Dose-dependent association between UGT1A1\*28 genotype and irinotecan-induced neutropenia: low doses also increase risk. *Clin Cancer Res* 2010;16:3832–42. <https://doi.org/10.1158/1078-0432.CCR-10-1122>.
- [16] 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>.

- [17] Liu XH, Lu J, Duan W, Dai ZM, Wang M, Lin S, et al. Predictive value of UGT1A1\*28 polymorphism in irinotecan-based chemotherapy. *J Cancer* 2017;8:691–703. <https://doi.org/10.7150/jca.17210>.
- [18] Hu ZY, Yu Q, Zhao YS. Dose-dependent association between UGT1A1\*28 polymorphism and irinotecan-induced diarrhoea: a meta-analysis. *Eur J Cancer* 2010;46:1856–65. <https://doi.org/10.1016/j.ejca.2010.02.049>.
- [19] Swen JJ, Nijenhuis M, van Rhenen M, de Boer-Veger NJ, Buunk AM, Houwink EJF, et al. Pharmacogenetic information in clinical guidelines: the European perspective. *Clin Pharmacol Ther* 2018;103:795–801. <https://doi.org/10.1002/cpt.1049>.
- [20] Marcuello E, Páez D, Paré L, Salazar J, Sebio A, Del Rio E, et al. A genotype-directed phase I-IV dose-finding study of irinotecan in combination with fluorouracil/leucovorin as first-line treatment in advanced colorectal cancer. *Br J Cancer* 2011;105:53–7. <https://doi.org/10.1038/bjc.2011.206>.
- [21] Goetz MP, McKean HA, Reid JM, Mandrekar SJ, Tan AD, Kuffel MA, et al. UGT1A1 genotype-guided phase I study of irinotecan, oxaliplatin, and capecitabine. *Invest N Drugs* 2013;31:1559–67. <https://doi.org/10.1007/s10637-013-0034-9>.
- [22] Denlinger CS, Blanchard R, Xu L, Bernaards C, Litwin S, Spittle C, et al. Pharmacokinetic analysis of irinotecan plus bevacizumab in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 2009;65:97–105. <https://doi.org/10.1007/s00280-009-1008-7>.
- [23] NCI. Common Terminology Criteria for Adverse Events. n.d. <https://doi.org/10.32388/erjxiq>.
- [24] Mathijssen RHJ, Verweij J, Loos WJ, De Bruijn P, Nooter K, Sparreboom A. Irinotecan pharmacokinetics-pharmacodynamics: the clinical relevance of prolonged exposure to SN-38. *Br J Cancer* 2002;87:144–50. <https://doi.org/10.1038/sj.bjc.6600447>.
- [25] De Jonge MJA, Verweij J, De Bruijn P, Brouwer E, Mathijssert RHJ, Van Alphen RJ, et al. Pharmacokinetic, metabolic, and pharmacodynamic profiles in a dose-escalating study of irinotecan and cisplatin. *J Clin Oncol* 2000;18:195–203. <https://doi.org/10.1200/JCO.2000.18.1.195>.
- [26] Shulman K, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowitz F, et al. Clinical implications of UGT1A1\*28 genotype testing in colorectal cancer patients. *Cancer* 2011;117:3156–62. <https://doi.org/10.1002/cncr.25735>.
- [27] McLeod HL, Sargent DJ, Marsh S, Green EM, King CR, Fuchs CS, et al. Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741. *J Clin Oncol* 2010;28:3227–33. <https://doi.org/10.1200/JCO.2009.21.7943>.
- [28] Kweekel DM, Gelderblom H, Van Der Straaten T, Antonini NF, Punt CJA, Guchelaar HJ. UGT1A1\*28 genotype and irinotecan dosage in patients with metastatic colorectal cancer: a Dutch Colorectal Cancer Group study. *Br J Cancer* 2008;99:275–82. <https://doi.org/10.1038/sj.bjc.6604461>.
- [29] Parodi L, Pickering E, Cisar LA, Lee D, Soufi-Mahjoubi R. Utility of pretreatment bilirubin level and UGT1A1 polymorphisms in multivariate predictive models of neutropenia associated with irinotecan treatment in previously untreated patients with colorectal cancer. *ADI* 2008;1:97–106. <https://doi.org/10.1111/j.1753-5174.2008.00014.x>.
- [30] Toffoli G, Cecchin E, Corona G, Russo A, Buonadonna A, D'Andrea M, et al. The role of UGT1A1\*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006;24:3061–8. <https://doi.org/10.1200/JCO.2005.05.5400>.
- [31] Braun MS, Richman SD, Thompson L, Daly CL, Meade AM, Adlard JW, et al. Association of molecular markers with toxicity outcomes in a randomized trial of chemotherapy for advanced colorectal cancer: the FOCUS trial. *J Clin Oncol* 2009;27:5519–28. <https://doi.org/10.1200/JCO.2008.21.6283>.
- [32] Roncato R, Cecchin E, Montico M, De Mattia E, Giodini L, Buonadonna A, et al. Cost evaluation of irinotecan-related toxicities associated with the UGT1A1\*28 patient genotype. *Clin Pharmacol Ther* 2017;102:123–30. <https://doi.org/10.1002/cpt.615>.
- [33] Gold HT, Hall MJ, Blinder V, Schackman BR. Cost effectiveness of pharmacogenetic testing for uridine diphosphate glucuronosyltransferase 1A1 before irinotecan administration for metastatic colorectal cancer. *Cancer* 2009;115:3858–67. <https://doi.org/10.1002/cncr.24428>.
- [34] Obradovic M, Mrhar A, Kos M. Cost-effectiveness of UGT1A1 genotyping in second-line, high-dose, once every 3 weeks irinotecan monotherapy treatment of colorectal cancer. *Pharmacogenomics* 2008;9:539–49. <https://doi.org/10.2217/14622416.9.5.539>.
- [35] Butzke B, Oduncu FS, Severin F, Pfeufer A, Heinemann V, Giesen-Jung C, et al. The cost-effectiveness of UGT1A1 genotyping before colorectal cancer treatment with irinotecan from the perspective of the German statutory health insurance. *Acta Oncol (Madr)* 2016;55:318–28. <https://doi.org/10.3109/0284186X.2015.1053983>.
- [36] Innocenti F, Schilsky RL, Ramírez J, Janisch L, Undevia S, House LK, et al. Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. *J Clin Oncol* 2014;32:2328–34. <https://doi.org/10.1200/JCO.2014.55.2307>.
- [37] Boisdron-Celle M, Metges JP, Capitain O, Adenis A, Raoul JL, Lecomte T, et al. A multicenter phase II study of personalized FOLFIRI-cetuximab for safe dose intensification. *Semin Oncol* 2017;44:24–33. <https://doi.org/10.1053/j.seminoncol.2017.02.007>.
- [38] Páez D, Tobeña M, Fernández-Plana J, Sebio A, Virgili AC, Cirera L, et al. Pharmacogenetic clinical randomised phase II trial to evaluate the efficacy and safety of FOLFIRI with high-dose irinotecan (HD-FOLFIRI) in metastatic colorectal cancer patients according to their UGT1A1 genotype. *Br J Cancer* 2019;120:190–5. <https://doi.org/10.1038/s41416-018-0348-7>.
- [39] Toffoli G, Cecchin E, Gasparini G, D'Andrea M, Azzarello G, Basso U, et al. Genotype-driven phase I study of irinotecan administered in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;28:866–71. <https://doi.org/10.1200/JCO.2009.23.6125>.
- [40] Hulshof EC, Deenen MJ, Guchelaar HJ, Gelderblom H. Pretherapeutic 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>.