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

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PART I

Implementation of *UGT1A1* genotype-guided dosing of irinotecan

CHAPTER 2

Pre-therapeutic *UGT1A1* genotyping to reduce the risk of irinotecan-induced severe toxicity: Ready for prime time

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ABSTRACT

Aim

Pre-therapeutic *UGT1A1* genotyping is not yet routinely performed in most hospitals in patients starting irinotecan chemotherapy. The aim of this position paper was to evaluate the available evidence and to assess the potential value of genotyping of *UGT1A1*28* and *UGT1A1*6* in patients before starting treatment with irinotecan in order to reduce the risk of severe toxicity.

Methods

Literature was selected and assessed based on five pre-specified criteria: 1] level of evidence for associations between *UGT1A1* polymorphisms and irinotecan-induced severe toxicity, 2] clinical validity and utility of pre-therapeutic genotyping of *UGT1A1*, 3] safety and tolerability of irinotecan in carriers of *UGT1A1* polymorphisms, 4] availability of specific dose recommendations for irinotecan in carriers of *UGT1A1* polymorphisms, 5] evidence of cost benefits of pre-therapeutic genotyping of *UGT1A1*.

Results

On all five criteria, study results were favourable for pre-therapeutic genotyping of *UGT1A1*. A high 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*. The clinical validity and utility of this genetic test 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 to save costs.

Conclusions

Pre-therapeutic genotyping of *UGT1A1* in patients initiating treatment with irinotecan improves patient safety and is likely to be cost-saving, and should therefore become standard of care.

INTRODUCTION

Irinotecan is a commonly applied anti-cancer drug that frequently leads to complications such as severe delayed diarrhoea and neutropenia. Irinotecan is registered for first-line treatment of pancreatic cancer, second-line treatment of colorectal cancer and is also used in other tumour types, such as Ewing sarcoma. Of all treated patients, up to 40% experience CTC grade ≥3 delayed diarrhoea, and up to 50% of the patients experience grade ≥3 neutropenia [1, 2].

Irinotecan is a prodrug that is activated via carboxylesterases in the liver and blood to SN-38, which in turn is glucuronidated in the liver and intestines into SN38-glucuronide (SN38-G) by UDP-glucuronosyltransferase 1A1 (UGT1A1). UGT1A1 is the main enzyme responsible for the inactivation of SN-38 [3].

Several genetic variants within the *UGT1A1* gene are known to be associated with reduced UGT1A1 enzyme activity, and therefore with an increased risk for irinotecan-related severe toxicity [4, 5]. The most well-characterized *UGT1A1* genetic variants are *UGT1A1*28* and *UGT1A1*6*. *UGT1A1*28* is a common tandem repeat polymorphism in the promotor region of the *UGT1A1* gene that leads to reduced enzyme activity, which is also known as Gilbert's syndrome [6, 7]. Homozygous carriers of these variants have a decreased UGT1A1 expression of up to 70% [7]. The polymorphism *UGT1A1*6* is a missense mutation and reduces UGT1A1 enzyme activity to an extent that is comparable to the effect of *UGT1A1*28* [8, 9]. The *UGT1A1*28* polymorphism is highly prevalent in the African, Latino and European population, with a minor allele frequency (MAF) ranging from 32% to 40%, whereas this polymorphism occurs less frequently in the East-Asian population (MAF 12%) and does not occur in the South-Asian population [10]. In contrast, the *UGT1A1*6* polymorphism has the highest MAF in the East-Asian population, i.e. 15%, compared to 0–5% in all other populations [10]. In the Chinese and Japanese population also a combined occurrence of *UGT1A1*6* and *UGT1A1*28* was reported with an incidence ranging from 3–8% [8, 11, 12]. A considerable amount of literature has been published on the association between *UGT1A1* polymorphism and severe toxicity of irinotecan, but so far, *UGT1A1* genotyping is not being routinely applied. Therefore, the aim of this position paper was to evaluate the available evidence and to assess the potential value of pre-therapeutic genotyping of *UGT1A1*28* and *UGT1A1*6* in patients indicated for treatment with irinotecan. The outcomes of this study are relevant for oncologists who prescribe irinotecan in daily practice and for their patients.

METHODS

A literature search was conducted to compile the available evidence on UGT1A1 genotyping in patients treated with irinotecan. We searched PubMed until March 2020 without any limitations on publication year using the following search terms: "irinotecan", "CPT-11", "pharmacogenetics", "cost-effectiveness", "cost-analysis", "UGT1A1", "UGT1A1*6" and "UGT1A1*28". Reference lists in original articles and review articles were manually searched to identify additional potentially relevant publications. In addition, we screened all the available drug labels and guidelines on irinotecan provided on PharmGKB [13].

Publications were included if they reported on at least one of the following subjects: 1] the association between irinotecan-related toxicity and carriership of *UGT1A1*6* or *UGT1A1*28*; 2] *UGT1A1* genotype-guided dose-finding studies for irinotecan; 3] dose recommendations on drug labels or in guidelines for the administration of irinotecan in carriers of *UGT1A1*6* or *UGT1A1*28*; or 4] cost-evaluation of pre-therapeutic *UGT1A1*6* or *UGT1A1*28* genotyping. Publications reporting on liposomal irinotecan were excluded.

To assess the available evidence for pre-therapeutic genotyping of *UGT1A1* in patients treated with irinotecan in a structured and objective manner, data were assessed based on five main criteria, in accordance with standardized guidelines [14–16] on assessing the clinical validity and clinical utility of pharmacogenetic testing.

1. Level of evidence for the association between *UGT1A1* polymorphisms and irinotecan-induced severe toxicity

The following toxicity endpoints were assessed: grade ≥3 neutropenia, grade ≥3 diarrhoea, febrile neutropenia, irinotecan-related hospital admissions, and death. If available, odds ratios or relative risks were reported for each endpoint. The level of evidence for each endpoint was assessed according to the standard operating procedures of the European Society of Medical Oncology [17]. The levels range from V to I, in which level I is the highest level of evidence.

2. Clinical validity and utility of pre-therapeutic genotyping of *UGT1A1*

The clinical validity of pre-therapeutic genotyping of *UGT1A1* describes the accuracy of this genetic test to identify a patient's risk to develop severe toxicity [16]. The clinical validity was assessed by calculating the sensitivity, the specificity and the positive and negative predictive value. In general, a low sensitivity may be expected since other (genetic) factors are also

known to be predictive for irinotecan-induced toxicity and not all toxicity may be attributed to only one single polymorphism.

The clinical utility of pre-therapeutic genotyping of *UGT1A1* describes the ability of genotyping to prevent severe toxicity through differentiation in treatment based on the genotyping results. The clinical utility was assessed by calculating the number needed to treat (NNT; i.e. to apply a dose reduction) and the number needed to genotype (NNG) [14].

Clinical validity and utility parameters were calculated for both *UGT1A1*6* and *UGT1A1*28* for the most important adverse events, that is, grade ≥3 diarrhoea and neutropenia in a recessive genetic model: homozygous versus heterozygous plus wild type.

Since there are no clear cut-off values for deciding whether pre-therapeutic genotyping of *UGT1A1* is clinically valid and utile, values were also compared to the genotype test recently recommended by the European Medicines Agency for the pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines [18]. A position paper by Lunenburg et al. presented the clinical validity and utility parameters for this genotype test, these parameters were calculated for *DPYD*2A* and *c.2846A>T* for grade ≥3 toxicity [19].

3. Safety and tolerability of irinotecan in carriers of *UGT1A1* polymorphisms

All available *UGT1A1* genotype-guided dose-finding studies for irinotecan were collected. To compare the outcomes of all the identified studies, relative dose intensities were calculated per study and genotype category and reported in a forest plot. These relative dose intensities were calculated by dividing the recommended dose or maximum tolerable dose reported in each study by the standard conventional dose of irinotecan conform the treatment schedule used in each study, multiplied by 100%.

4. Availability of specific dose recommendations for irinotecan in carriers of *UGT1A1* polymorphisms

Specific dose recommendations per *UGT1A1* genotype category are necessary to provide guidance for oncologists in applying *UGT1A1* genotype-guided dosing. Drug labels and clinical guidelines were screened for the presence of specific dose recommendations per *UGT1A1* genotype category.

5. Evidence of cost benefits of pre-therapeutic genotyping of *UGT1A1*

The implementation of pre-therapeutic *UGT1A1* genotyping will increase treatment costs due to the extra costs for genotyping, but it might also be cost-saving due to the reduction of severe irinotecan-induced toxicity and hospitalisation. All the available cost-analysis publications on pre-therapeutic *UGT1A1* genotyping were assessed.

RESULTS

Based on the selection criteria, a total of 41 publications, 4 drug labels and 3 guidelines were included, specifically resulting in a total of 23, 1, 12, 7 and 5 included publications for criteria 1–5, respectively.

1] Level of evidence for the association between *UGT1A1* polymorphisms and irinotecan-induced severe toxicity

A considerable amount of literature has been published on the increased risk for irinotecan-related toxicity in homozygous *UGT1A1*28* variant allele carriers; this increased risk has been demonstrated in case reports on several [20], sometimes even lethal adverse events [21, 22], in multiple retro- and prospective genetic association studies [23–25] and also in several meta-analyses [26–30]. A similar increased risk for irinotecan-related toxicity in homozygous *UGT1A1*6* variant allele carriers has been reported in several genetic association studies [31–33] and several meta-analyses [34–38].

Carriership of a *UGT1A1* polymorphism was highly associated with grade ≥3 neutropenia and grade ≥3 diarrhoea (level of evidence I). For *UGT1A1*28*, the largest effect size was seen in homozygous carriers compared to heterozygous and wild type patients (recessive model): four [26–29] out of five [26–29, 34] meta-analyses showed a two- to four-fold increased risk of grade ≥3 neutropenia. In all three meta-analyses on *UGT1A1*6*, a similar increased neutropenia risk was observed [34, 35, 37]. For *UGT1A1*28*, a two- to six-fold increased risk of grade ≥3 diarrhoea was observed in four [28–30, 34] out of five [26, 28–30, 34] meta-analyses; in addition, the effect size seemed larger in patients treated at medium or higher doses of irinotecan (>125 mg/m^2). In three meta-analyses reporting on *UGT1A1*6* and severe diarrhoea, homozygotes had a three- to four-fold increased risk compared to wild type patients [36, 38] and a four-fold increased risk compared to heterozygous and wild type patients [34]. A more detailed description of all meta-analyses of studies on the association of *UGT1A1* polymorphisms and grade ≥3 neutropenia and diarrhoea is provided in **Tables 2.1a** and **2.1b**.

Table 2.1a: Association between irinotecan-related severe neutropenia and *UGT1A1* polymorphism

				Association with irinotecan grade ≥ III neutropenia				
Group	n total	Ethnicity	Polymorphism	Comparison	n	Dose (mg/m²)	OR	95% CI
Hoskins et al. 2007 [26]	821	Caucasian	*28	HO vs HE+WT	229	100–125	1.80	0.37–8.84
					410	180	3.22	1.52–6.81
					184	200 – 350	27.8	4.0–195
Hu et al. 2010 [27]	1998	Mainly Caucasian	*28	HO vs HE+WT	1998	80–350	2.20*	1.82–2.66
					300	<150	2.43*	1.34–4.39
					1481	150–250	2.00*	1.62–2.47
					217	≥250	7.22*	3.10–16.78
				HE vs WT	1738	80–350	1.43*	1.16–1.77
					270	<150	2.94*	1.36–6.35
					1288	150–250	1.29*	1.04–1.62
					180	≥250	2.65*	0.70–9.94
Liu et al. 2014 [28]	2015	Caucasian	*28	HO vs HE+WT	2015	80–350	3.44	2.45–4.82
					704	<150	3.63	2.02–6.53
					1311	≥150	3.34	2.21–5.05
				HO vs WT	1095	80–350	4.79	3.28–7.01
					331	<150	6.37	2.69–10.71
					764	≥150	4.64	2.88–7.17
				HE vs WT	1819	80–350	1.90	1.44–2.51
					630	<150	2.01	1.21–3.34
					1189	≥150	1.85	1.32–2.58
Han et al. 2014 [35]	994	Asian	*6	HO vs HE+WT	984	50–350	3.28	1.89–5.69
				HO+HE vs WT	994	50–350	1.54	1.18–2.04
			*6/*28	HO+*6/*28 vs HE+WT	923	50–350	3.28	2.15–4.98

Table 2.1a continues on next page.

Table 2.1a: ***Continued***

				Association with irinotecan grade ≥ III neutropenia				
Group	n total	Ethnicity	Polymorphism	Comparison	n	Dose (mg/m^2)	OR	95% CI
Cheng et al. 2014 [36]	1027	Asian	*6	HO vs WT	576	30–180	4.44	2.42–8.14
					116	<150	9.64	2.05–45.28
					460	≥150	3.95	2.05–7.64
				HE vs WT	933	30–180	1.98	1.45–2.71
					249	<150	4.42	2.27–8.59
					684	≥150	1.55	1.08–2.22
Liu et al. 2017 [29]	6087	Asian and Caucasian	*28	HO vs HE+WT	3668	60–350	4.12	2.36–7.20
				HO+HE vs WT	5232	60–350	2.15	1.71–2.70
				HO vs WT	3575	60–350	5.34	3.05–9.33
				HE vs WT	3948	60–350	1.71	1.41–2.08
Chen et al. 2017 [34]	577	Asian	*6	HO vs HE+WT	277	50–100	4.80	1.62–14.27
				HO+HE vs WT	233	50–100	2.40	1.28–4.49
				HO vs WT	58	50–100	2.16	0.28–16.96
				HE vs WT	182	50–100	2.09	0.66–6.62
			*28	HO vs HE+WT	101	50–100	1.27	0.20–7.94
				HO+HE vs WT	494	50–100	1.47	0.90–2.42
				HO vs WT	45	50–100	1.27	0.20–7.95
				HE vs WT	412	50–100	1.50	0.86–2.62

Table 2.1a: *Continued*

				Association with irinotecan grade ≥ III neutropenia				
Group	n total	Ethnicity	Polymorphism	Comparison	n	Dose (mg/m^2)	OR	95% CI
Zhang et al. 2017 [37]	1140	Asian	*6	HO+HE vs WT	n.r	60–225	2.03	1.54–2.68
					n.r.	<150	2.66	1.10–6.45
					n.r.	≥150	1.97	1.45–2.67
				HO vs WT	n.r.	60–225	2.95	1.83–4.75
					n.r.	<150	3.17	1.11–9.04
					n.r.	≥150	2.89	1.69–4.94
				HE vs WT	n.r.	60–225	1.83	1.36–2.46
					n.r.	<150	2.36	1.28–4.35
					n.r.	≥150	1.65	1.15–2.35
Yang et al. 2018 [38]	6742	Asian	*6	HO vs WT	1466	50–350	3.03	2.05–4.47
				HE vs WT	1928	50–350	1.95	1.34–2.85
		Asian and Caucasian	*28	HO vs WT	2609	50–350	3.50	2.23–5.50
				HE vs WT	3516	50–350	1.91	1.45–2.50

* RR instead of OR. CI = confidence interval, HE = heterozygous carrier, HO = homozygous carrier, n.r. = not reported, OR = odds ratio, RR = relative risk, WT = wild type.

Table 2.1b: Association between irinotecan-related severe diarrhoea and *UGT1A1* polymorphism

				Association with irinotecan grade ≥ III diarrhoea				
Group*	n total	Ethnicity	Polymorphism	Comparison	n	Dose (mg/m^2)	OR	95% CI
Hu et al. 2010 [30]	1065	Asian and Caucasian	*28	HO vs HE+WT	1760	60–350	1.81	1.38–2.39
					355	≤125	1.06	0.57–1.99
					1405	>125	2.06	1.51–2.80
				HE vs WT	1265	60–350	1.73	1.25–2.40
					335	≤125	1.27	0.67–2.42
					930	>125	1.92	1.31–2.82
Liu et al. 2014 [28]	2015	Caucasian	*28	HO vs HE+WT	1980	80–350	1.71	1.18–2.47
					663	<150	1.41	0.82–2.43
					1317	≥150	2.04	1.23–3.38
				HO vs WT	1122	80–350	1.84	1.24–2.72
					348	<150	1.41	0.79–2.51
					774	≥150	2.37	1.39–4.04
				HE vs WT	1794	80–350	1.20	0.93–1.56
					593	<150	1.02	0.70–1.50
					1201	≥150	1.39	0.97–1.98
Cheng et al. 2014 [36]	1027	Asian	*6	HO vs WT	470	30–180	3.51	1.41–7.83
				HE vs WT	719	30–180	1.44	0.84–2.49

Table 2.1b: ***Continued***

				Association with irinotecan grade ≥ III diarrhoea				
Group*	n total	Ethnicity	Polymorphism	Comparison	n	Dose (mg/m^2)	OR	95% CI
Chen et al. 2017 [34]	577	Asian	*6	HO vs HE+WT	307	50–100	6.25	1.51–25.0
				HO+HE vs WT	186	50–100	1.45	0.74–2.84
				HO vs WT	80	50–100	5.93	1.46–24.0
				HE vs WT	182	50–100	1.33	0.60–2.91
			*28	HO vs HE+WT	131	50–100	4.56	1.56–13.18
				HO+HE vs WT	447	50–100	4.90	2.02–11.88
				HO vs WT	104	50–100	17.64	2.58–120.66
				HE vs WT	439	50–100	4.36	1.74–10.91
Yang et al. 2018 [38]	6742	Asian	*6	HO vs WT	651	50–350	4.03	1.98–8.32
				HE vs WT	844	50–350	1.98	1.26–3.11
		Asian and Caucasian	*28	HO vs WT	1817	50–350	1.69	1.20–2.40
				HE vs WT	2521	50–350	1.45	1.07–1.97

* Hoskins et al. did not find an association between irinotecan-related diarrhoea and homozygous carriers of UGT1A1*28, an OR was not reported [26]. CI = confidence interval, HE = heterozygous carrier, HO = homozygous carrier, OR = odds ratio, RR = relative risk, WT = wild type.

Level III and IV evidence was available for the association between *UGT1A1*28* and febrile neutropenia [39–42]. One study reporting on the administration of low doses of irinotecan (50–60 mg/m^2) could not replicate this increased risk [43]. For *UGT1A1*6*, one small study (n=69) reported on an increased risk of febrile neutropenia in heterozygous carriers compared to wild type patients [44].

The carriership of a *UGT1A1*28* allele also increased the risk of hospitalisation due to toxicity (level of evidence III & IV) [39, 41]. No studies on this endpoint have been reported for *UGT1A1*6*. The *UGT1A1*28* variant may also be associated with treatment-related mortality (level of evidence IV); treatment-related fatal neutropenia and bacteraemia occurred in 2 out of 102 (2%) wild type patients compared to 3 out of 26 (11.5%) heterozygous or homozygous *UGT1A1*28* carriers ($p<0.01$) [39]. No studies on *UGT1A1*6* reported on this endpoint.

2] Clinical validity and utility of pre-therapeutic genotyping of *UGT1A1*

The clinical validity and utility parameters were based on event rates reported in the meta-analysis by Yang et al. We selected this meta-analysis because it included Asian as well as Caucasian patients with data on *UGT1A1*6* and *UGT1A1*28*, respectively; besides, it included the highest number of patients and it was the most recent of all the identified meta-analyses [38].

The calculated sensitivity, specificity and positive and negative predictive values for pre-therapeutic *UGT1A1* genotyping are provided in **Table 2.2**. The values proved to be comparable with the values of pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines [19]. These numbers indicate that pre-therapeutic *UGT1A1* genotyping would not identify all patients that experienced severe diarrhoea or neutropenia, but it would identify almost all the patients that had a good ability to tolerate irinotecan. This test may have false positive results, which may lead to a dose reduction of irinotecan, but this risk is unlikely to be relevant since only the starting dose of irinotecan will be reduced, followed by dose optimisation based on the tolerability of irinotecan in each individual patient. The low number of false negatives is of the highest importance, since the expected severe toxicity of irinotecan in these patients can lead to hospitalisation and delay or even discontinuation of treatment, resulting in a reduced quality of life and treatment failure.

Additionally, the NNT and NNG were calculated. For *UGT1A1*28*, the NNT (i.e. apply a dose reduction) to prevent ≥ grade 3 neutropenia was 9 and to prevent ≥ grade 3 diarrhoea was 14. The NNG to prevent ≥ grade 3 neutropenia and ≥ grade 3 diarrhoea was 79 and 127,

respectively. In view of these results, pre-therapeutic genotyping of *UGT1A1*28* seems even more clinically utile than pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines, which is mainly due to the higher prevalence of *UGT1A1*28*. For *UGT1A1*6*, the NNT to prevent ≥ grade 3 neutropenia was 8 and the NNT to prevent ≥ grade 3 diarrhoea was 11, while the NNG was 376 and 564, respectively. *UGT1A1*6* seems less clinically utile than pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines because of the high NNG, which is caused by the low prevalence of this polymorphism. Only 2% of the East-Asian population are homozygous carriers of this polymorphism, and the polymorphism is not present in other populations. See **Table 2.2** for a detailed overview.

Table 2.2: Clinical validity and utility of pre-therapeutic genotyping of *UGT1A1* in patients treated with irinotecan compared to the clinical validity and utility of *DPYD* in patients treated with fluoropyrimidines

	*UGT1A1*6* [38]		*UGT1A1*28* [38]		*DPYD* variants [19]
Parameter	≥ grade 3 neutropenia	≥ grade 3 diarrhoea	≥ grade 3 neutropenia	≥ grade 3 diarrhoea	≥ grade 3 toxicity
Sensitivity	11%	11%	11%	13%	12–15%
Specificity	94%	94%	94%	92%	98%
PPV	33%	20%	30%	22%	20–24%
NPV	80%	89%	82%	85%	96–97%
NNG	376	564	79	127	210–251
NNT	8	11	9	14	5–6

NNG = number needed to genotype, NNT = number needed to treat, NPV = negative predictive value, PPV = positive predictive value.

3] Safety and tolerability of irinotecan in carriers of *UGT1A1* polymorphisms

Several phase 1 *UGT1A1* genotype-guided dose-finding studies have been conducted. In these studies, the maximum tolerable dose (MTD) most often was lower than the standard dose of irinotecan in homozygous carriers of *UGT1A1*6* or *UGT1A1*28* or in compound heterozygous carriers (*UGT1A1*6/*28*) (**Figure 2.1** + **Supplementary Material Table S2.1**). Five [45–49] out of six of these dose-finding studies found a lower MTD than the registered dose of irinotecan and therefore suggest to lower the irinotecan starting dose, with relative dose intensities ranging from 42 to 83% [22, 45–49]. Moreover, the single study that reported a 100% relative dose intensity stated that homozygous carriers may receive irinotecan at a starting dose of 150 mg/m^2, but in subsequent cycles dose reductions or treatment delays were indicated in 12 out of 16 patients (75%) [22].

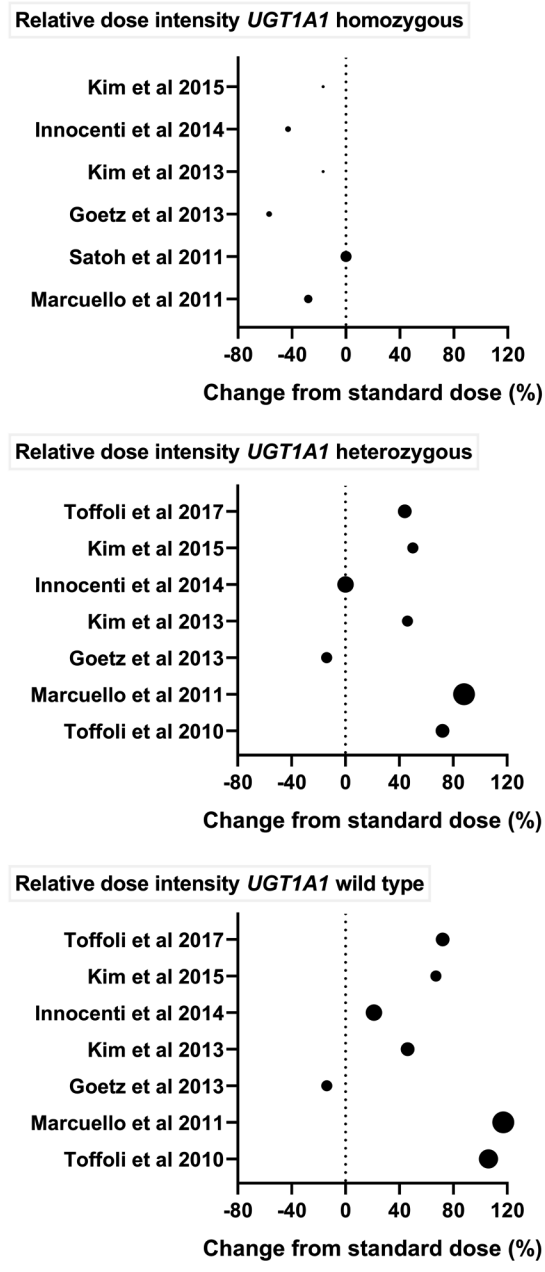

Figure 2.1: Forest-plot of outcomes of dose-finding studies of irinotecan per *UGT1A1* genotype category [22, 45–51].
Each dot represents the outcome of one study, presented as the difference between the maximum tolerable dose (MTD) reported and the standard dose of irinotecan in percentages. The size of each dot indicates the number of patients in each study in comparison to the other studies. Top: homozygous carriers of *UGT1A1*6* or *UGT1A1*28*, middle: heterozygous carriers of *UGT1A1*6* or *UGT1A1*28*, bottom: wild type patients. For the exact numbers see Table S2.1 in the Supplementary material.

In heterozygous carriers of *UGT1A1*6* or *UGT1A1*28* and wild type patients, the MTD was often higher than the standard dose. Five [45, 47, 49–51] out of seven and six [45, 47–51] out of seven dose-finding studies found a higher MTD than the standard dose in heterozygous carriers and wild type patients, with relative dose intensities ranging from 86 to 188% and 86 to 217%, respectively [45–51]. Most of the patients in these dose-finding studies had a relatively low ECOG performance score (ranging from 0 to 1) compared to the real-world population, which might have led to overestimation of the MTD.

Three prospective genotype-guided dosing studies tested the reduced starting dose of irinotecan for homozygous carriers of *UGT1A1*6* or *UGT1A1*28* or *UGT1A1*6/*28* [11, 52, 53] and their findings are in line with the dose-finding studies presented in **Figure 2.1**. Fuji et al. reduced the starting dose of irinotecan from 150 mg/m^2 to 120 mg/m^2 (relative dose intensity 80%) in the homozygous group (n=10), finding no significant differences in adverse events or tumour response compared to the heterozygous carriers and wild type patients (n=43) in this study [11]. Xu et al. conducted a preplanned analysis in the AXEPT trial (XELIRI or FOLFIRI schedule, n=650). Fifty homozygous carriers of *UGT1A1*6* or *UGT1A1*28* or *UGT1A1*6/*28* were enrolled, the starting dose of irinotecan was reduced to 150 mg/m^2 and was well tolerated [53]. Boisdron-Celle et al. conducted a proof of concept trial in which patients intended to be treated with FOLFIRI-cetuximab were stratified by their *UGT1A1*28* genotype and received irinotecan dose intensification provided that treatment was well-tolerated. Eighty-five patients were enrolled, and mean irinotecan doses at 3 months were 247, 210, and 140 mg/m^2 for wild type, heterozygous and homozygous carriers, respectively (relative dose intensities: 137%, 116% and 78%, respectively) [52].

Currently, there is one randomized controlled trial in which 82 wild type patients and heterozygous carriers of *UGT1A1*28* were randomised to receive either high dose-FOLFIRI or standard FOLFIRI [54]. In the high dose-FOLFIRI group, the irinotecan dose was 300 mg/m^2 for wild type patients and 260 mg/m^2 for heterozygous patients. In the control group, the dose was 180 mg/m^2, irrespective of genotype. The authors concluded that *UGT1A1* wild type patients and heterozygous carriers of *UGT1A1*28* may receive higher doses of irinotecan and showed a higher objective response rate compared to those receiving the standard dose (67.5 versus 43.6%; OR=1.73 [95% CI:1.03–2.93, p=0.001]), without a significantly increased risk for severe toxicity (22.5% versus 20.5%).

Table 2.3: Overview of recommendations on drug labels and in guidelines for dosing of irinotecan in homozygous carriers of *UGT1A1* polymorphisms

Organisation	Country/ region	Dose reduction recommended for UGT1A1 polymorphisms?		Dose recommendation	References
Drug labels		*6	*28		
FDA	USA	No	Yes	≥1 dose level reduction	[55]
CBG-MEB	Netherlands	No	No	Not applicable	[60]
PMDA	Japan	Yes	Yes	No specification	[56]
HCSC	Canada	No	Yes	No specification	[57]
Guidelines					
RNPGx-GPCO-unicancer	France	No*	Yes	Dose 180–230 mg/m^2: 25–30% dose reduction Dose ≥240 mg/m^2: contra-indicated	[58]
KNMP-DPWG	Netherlands	Yes	Yes	30% dose reduction	[59]

* The authors mention that this analysis is limited by the fact that other *UGT1A1* deficient variants are relevant in non-Caucasian populations, particularly the *6 and *27 alleles in Asian populations. FDA = Food and Drug Administration, CBG-MEB = Dutch Medicines Evaluation Board, PMDA = Pharmaceuticals and Medical Devices Agency, HCSC = Health Canada/Santé Canada, RNPGx = National Pharmacogenetics Network, GPCO = Group of Clinical Onco-pharmacology, KNMP = Royal Dutch Association for the Advancement of Pharmacy, DPWG = Dutch Pharmacogenetics Working Group.

4] Availability of dose recommendations for irinotecan in carriers of *UGT1A1* polymorphisms

Various dose recommendations for irinotecan in homozygous carriers of *UGT1A1*28* were found on drug labels and in guidelines (**Table 2.3**). Most of the national medicines authorities and guideline working groups recommend to apply a dose reduction of 25 to 30% in homozygous carriers of *UGT1A1*28* [55–59]. Only the Dutch national medicines authority does not recommend dose reduction in homozygous carriers of *UGT1A1*28* treated with conventional irinotecan [60].

For homozygous carriers of *UGT1A1*6*, less information was found on drug labels and in guidelines, which might be due to the fact that this polymorphism only occurs in the Asian population. However, the Japanese drug label states that patients should be selected for treatment based on their stage, general condition and *UGT1A1* genotype, although no specific dose recommendations are provided [56].

Only the French working group mentions dose recommendations for *UGT1A1*28* heterozygous and wild type patients, stating that the administration of an intensified dose of irinotecan (240 mg/m^2) is only possible in wild type patients. In heterozygous patients, dose intensification may be applied in the absence of additional risk factors and under strict medical surveillance [58]. Obviously, this is an off-label dose recommendation.

Moreover, the Clinical Pharmacogenetics Implementation Consortium assigned level A to this gene-drug interaction, indicating that genetic information should be used to change the prescription of this drug [61].

5] Evidence of cost-benefits of pre-therapeutic genotyping of *UGT1A1*

Besides improved patient safety, pre-therapeutic genotyping of *UGT1A1* is also likely to be cost-effective or even cost-saving. To date, four studies [62–65] assessed the cost effectiveness of pre-therapeutic genotyping followed by a 20% to 25% dose reduction of irinotecan in homozygous variant carriers of *UGT1A1*28* in Caucasian populations, or in carriers of both *UGT1A1*6* and *UGT1A1*6/*28* in a Chinese population, compared to no genotyping. This was assessed with decision-analytic models using clinical and genetic data from literature. All studies concluded that pre-therapeutic genotyping was a cost-saving strategy compared to no genotyping, reporting cost reductions due to pre-therapeutic genotyping ranging from 112 euro up to 596 euro per patient.

Roncato et al. [66] conducted the first retrospective clinical validation study in an Italian hospital setting. They assessed the association between the *UGT1A1*28* genotype and the cost of toxicity management. The mean costs per patient were 812€ for wildtype patients, 1,119€ for heterozygous variant carriers, and 4,886€ for homozygous variant carriers, which illustrates that the costs of irinotecan-related toxicity are significantly higher in patients carrying a homozygous or heterozygous variant of *UGT1A1*28* than in wild type patients. The cost driver was hospitalisation, which accounted for 82% of all toxicity costs. Six out of 22 (27%) homozygous variant carriers were hospitalised for irinotecan-related toxicity, compared to 10 out of 122 (8.2%) heterozygous variant carriers and 6 out of 109 (5.5%) wild type patients.

DISCUSSION

Based on the available literature, we conclude that pre-therapeutic genotyping of *UGT1A1* in patients initiating treatment with irinotecan improves patient safety and is likely to be cost-saving. In this review, the available evidence for pre-therapeutic genotyping of *UGT1A1*6* and *UGT1A1*28* in patients treated with irinotecan was assessed in a structured and objective manner, and data were assessed based on five main criteria.

Level of evidence I exists for the association of *UGT1A1*28* and *UGT1A1*6* and irinotecan-induced severe neutropenia or severe diarrhoea; level III for the association between *UGT1A1*28* and febrile neutropenia, and level III and IV for treatment-related hospitalisation and mortality, respectively. In addition, the clinical validity and utility of pre-therapeutic genotyping of *UGT1A1* proved to be acceptable and comparable with the clinical validity and utility of pre-therapeutic genotyping of *DPYD* in patients treated with fluoropyrimidines. Since this *DPYD* test has recently been recommended by the EMA [18], pre-therapeutic *UGT1A1* genotyping might also be considered clinically valid and utile.

Moreover, the combined conclusion of multiple dose-finding studies indicate that the current standard way of dosing of irinotecan is not safe for homozygous carriers of *UGT1A1*6* or *UGT1A1*28*, whereas wild type patients might even tolerate higher doses of irinotecan. A complementing finding is that the evidence described above has been taken up in various drug labels and guidelines providing specific dose recommendations for irinotecan in homozygous carriers of *UGT1A1*28* or *UGT1A1*6*: most of the national medicines authorities and guideline working groups recommend to apply an initial dose reduction of 25 to 30% in these patients.

Finally, pre-therapeutic genotyping of *UGT1A1* is likely to be cost-saving. Homozygous carriers of *UGT1A1*28* or *UGT1A1*6* were shown to have ~6-fold higher irinotecan-related toxicity costs than wild type patients, mainly due to costs for hospitalisation for toxicity treatment. In comparison, patients carrying a *DPYD* variant seem to have ~4-fold higher toxicity costs than wild type patients [67]. This indicates that the costs of pre-therapeutic genotyping seem to be outweighed by the savings achieved by preventing the costs of toxicity treatment.

A limitation on the available evidence for *UGT1A1* genotype-guided dosing of irinotecan is the absence of a randomized controlled trial on treatment outcome, i.e. overall survival. However, such a trial is hardly feasible and is not likely to be conducted, since at least a roughly estimated 300 homozygous individuals per arm would be needed for sufficient power, requiring a total of at least 6000 patients to be prospectively screened for inclusion. Moreover, with the available evidence favouring pre-therapeutic genotyping, it seems not ethical to randomise patients and patients may not be willing to participate in such a trial. Nonetheless, it is unlikely that genotype-guided dosing for homozygous carriers of *UGT1A1*28* or *UGT1A1*6* will negatively affect overall survival, since the recommended dose reduction leads to equal systemic exposure to SN-38 in these patients as in wild type patients treated with standard-dose therapy [46,68]. Moreover, the addition of other *UGT1A1* variants such as *UGT1A1*93* [4] and variants of other genes encoding for other enzymes such as *UGT1A7* and *UGT1A9* [69] might improve the predictive ability of *UGT1A1* genotype-guided dosing of irinotecan. Of interest, a prospective *UGT1A1*93* genotype-guided dose-finding trial is currently ongoing (https://www.trialregister.nl/ - trial NL6270 (NTR6612)).

Overall, based on this evaluation, all five criteria that were assessed showed that the available evidence is in favour of pre-therapeutic genotyping of *UGT1A1*. We recommend that all patients starting with irinotecan chemotherapy should be genotyped for *UGT1A1*28*; for Asian patients, the *UGT1A1*6* polymorphism should be tested. If a patient is homozygous for *UGT1A1*28* or *UGT1A1*6*, a dose reduction of 25 to 30% should be performed for all dosing regimens of irinotecan. Patients that are compound heterozygous *UGT1A1*6/*28* are considered poor metaboliser. Although less data is available, the available studies and the Japanese drug label suggest to treat these patients conform homozygous carriers of *UGT1A1*6* [11, 22, 35, 56, 65]. Dose-escalation in wild type patients is potentially safe, but there is not enough literature on clinical outcomes, and hence further research is warranted. Due to the presence of a wide interpatient variability in the pharmacokinetic parameters of irinotecan, a step-up based approach based on therapeutic drug monitoring might be of interest [70]. In addition, although turn-around time and costs of *UGT1A1* genotyping may be a challenging issue,

integration of *UGT1A1* genotyping into tumour sequencing programs may potentially enable genome testing without additional genotyping costs [71].

In summary, we conclude that pre-therapeutic genotyping of *UGT1A1* followed by genotype-guided dosing in patients treated with irinotecan is to be favoured over standard treatment and should therefore become standard of care and be implemented in oncology guidelines, such as the NCCN and ESMO guidelines.

REFERENCES

[1] Rougier P, Bugat R. CPT-11 in the treatment of colorectal cancer: Clinical efficacy and safety profile. Semin Oncol 1996.

[2] Rothenberg M. Efficacy and toxicity of irinotecan in patients with colorectal cancer. Semin Oncol 1998;5:39–46.

[3] Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther 2012. https://doi.org/10.1038/clpt.2012.96.

[4] Crona DJ, Ramirez J, Qiao W, de Graan A-J, Ratain MJ, van Schaik RHN, et al. Clinical validity of new genetic biomarkers of irinotecan neutropenia: an independent replication study. Pharmacogenomics J 2015;16:1–6. https://doi.org/10.1038/tpj.2015.23.

[5] Onoue M, Terada T, Kobayashi M, Katsura T, Matsumoto S, Yanagihara K, et al. UGT1A1*6 polymorphism is most predictive of severe neutropenia induced by irinotecan in Japanese cancer patients. Int J Clin Oncol 2009;14:136–42. https://doi.org/10.1007/s10147-008-0821-z.

[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/NEJM199511023331802.

[8] Akiyama Y, Fujita K, Nagashima F, Yamamoto W, Endo H, Sunakawa Y, et al. Genetic testing for UGT1A1*28 and *6 in Japanese patients who receive irinotecan chemotherapy. Ann Oncol 2008:2089–90. https://doi.org/10.1093/annonc/mdn645.

[9] 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. https://doi.org/10.1097/FPC.0b013e328014341f.

[10] Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. Variation across 141,456 human exomes and genomes reveals the spectrum of loss-of-function intolerance across human protein-coding genes. BioRxiv 2019:531210. https://doi.org/10.1101/531210.

[11] Fujii H, Yamada Y, Watanabe D, Matsuhashi N, Takahashi T, Yoshida K, et al. Dose adjustment of irinotecan based on UGT1A1 polymorphisms in patients with colorectal cancer. Cancer Chemother Pharmacol 2019. https://doi.org/10.1007/s00280-018-3711-8.

[12] Bai Y, Wu HW, Ma X, Liu Y, Zhang YH. Relationship between UGT1A1*6/*28 gene polymorphisms and the efficacy and toxicity of irinotecan-based chemotherapy. Onco Targets Ther 2017. https://doi.org/10.2147/OTT.S137644.

[13] PharmGKB n.d. https://www.pharmgkb.org/chemical/PA450085/labelAnnotation (accessed May 8, 2020).

[14] Tonk ECM, Gurwitz D, Maitland-Van Der Zee AH, Janssens ACJW. Assessment of pharmacogenetic tests: Presenting measures of clinical validity and potential population impact in association studies. Pharmacogenomics J 2017;17:386–92. https://doi.org/10.1038/tpj.2016.34.

[15] Jansen ME, Rigter T, Rodenburg W, Fleur TMC, Houwink EJF, Weda M, et al. Review of the reported measures of clinical validity and clinical utility as arguments for the implementation of pharmacogenetic testing: A case study of statin-induced muscle toxicity. Front Pharmacol 2017;8. https://doi.org/10.3389/fphar.2017.00555.

[16] Burke W. Genetic tests: Clinical validity and clinical utility. Curr Protoc Hum Genet 2014. https://doi.org/10.1002/0471142905.hg0915s81.

[17] European Society for Medical Oncology. Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores 2020. https://www.esmo.org/content/download/77789/1426712/1 (accessed April 8, 2020).

[18] 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).

[19] Lunenburg CATC, Henricks LM, Guchelaar HJ, Swen JJ, Deenen MJ, Schellens JHM, et al. Prospective DPYD genotyping to reduce the risk of fluoropyrimidine-induced severe toxicity: Ready for prime time. Eur J Cancer 2016;54:40–8. https://doi.org/10.1016/j.ejca.2015.11.008.

[20] 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. https://doi.org/10.1155/2017/2683478.

[21] Rouits E, Boisdron-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.

[22] 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. https://doi.org/10.1111/j.1349-7006.2011.02030.x.

[23] 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.

[24] Massacesi C, Terrazzino S, Marcucci F, Rocchi MB, Lippe P, Bisonni 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.

[25] 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.

[26] Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. UGT1A1*28 genotype and irinotecan-induced neutropenia: Dose matters. J Natl Cancer Inst 2007. https://doi.org/10.1093/jnci/djm115.

[27] 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. https://doi.org/10.1158/1078-0432.CCR-10-1122.

[28] 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.

[29] 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. https://doi.org/10.7150/jca.17210.

[30] Hu ZY, Yu Q, Zhao YS. Dose-dependent association between UGT1A1*28 polymorphism and irinotecan-induced diarrhoea: A meta-analysis. Eur J Cancer 2010. https://doi.org/10.1016/j.ejca.2010.02.049.

[31] Nakamura Y, Soda H, Oka M, Kinoshita A, Fukuda M, Fukuda M, et al. Randomized Phase II Trial of Irinotecan with Paclitaxel or Gemcitabine for Non-small Cell Lung Cancer Association of UGT1A1*6 and UGT1A1*27 with Severe Neutropenia. vol. 6. 2011.

[32] Park SR, Kong SY, Rhee J, Park YI, Ryu KW, Lee JH, et al. Phase II study of a triplet regimen of S-1 combined with irinotecan and oxaliplatin in patients with metastatic gastric cancer: Clinical and pharmacogenetic results. Ann Oncol 2011;22:890–6. https://doi.org/10.1093/annonc/mdq435.

[33] Jada SR, Lim R, Wong CI, Shu X, Lee SC, Zhou Q, et al. Role of UGT1A1*6, UGT1A1*28 and ABCG2 c.421C>A polymorphisms in irinotecan-induced neutropenia in Asian cancer patients. Cancer Sci 2007;98:1461–7. https://doi.org/10.1111/j.1349-7006.2007.00541.x.

[34] Chen X, Liu L, Guo Z, Liang W, He J, Huang L, et al. UGT1A1 polymorphisms with irinotecan-induced toxicities and treatment outcome in Asians with Lung Cancer: a meta-analysis. Cancer Chemother Pharmacol 2017;79:1109–17. https://doi.org/10.1007/s00280-017-3306-9.

[35] 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.

[36] 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.

[37] Zhang X, Yin JF, Zhang J, Kong SJ, Zhang HY, Chen XM. UGT1A1*6 polymorphisms are correlated with irinotecan-induced neutropenia: a systematic review and meta-analysis. Cancer Chemother Pharmacol 2017;80:135–49. https://doi.org/10.1007/s00280-017-3344-3.

[38] 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. https://doi.org/10.1111/ajco.13028.

[39] Liu CY, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer 2008;112:1932–40. https://doi.org/10.1002/cncr.23370.

[40] Kweekel DM, Gelderblom H, Van der Straaten T, Antonini NF, Punt CJ, 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.

[41] Shulman K, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowicz 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.

[42] 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.

[43] Sugiyama T, Hirose T, Kusumoto S, Shirai T, Yamaoka T, Okuda K, et al. The UGT1A1*28 genotype and the toxicity of low-dose irinotecan in patients with advanced lung cancer. Oncol Res 2010. https://doi.org/10.3727/096504010X12626118079822.

[44] Oki E, Kato T, Bando H, Yoshino T, Muro K, Taniguchi H, et al. A Multicenter Clinical Phase II Study of FOLFOXIRI Plus Bevacizumab as First-line Therapy in Patients With Metastatic Colorectal Cancer: QUATTRO Study. Clin Colorectal Cancer 2018;17:147–55. https://doi.org/10.1016/j.clcc.2018.01.011.

[45] 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.

[46] 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 New Drugs 2013;31:1559–67. https://doi.org/10.1007/s10637-013-0034-9.

[47] Kim KP, Kim HS, Sym SJ, Bae KS, Hong YS, Chang HM, et al. A UGT1A1*28 and*6 genotype-directed phase i dose-escalation trial of irinotecan with fixed-dose capecitabine in Korean patients with metastatic colorectal cancer. Cancer Chemother Pharmacol 2013. https://doi.org/10.1007/s00280-013-2161-6.

[48] Innocenti F, Schilsky RL, Ramirez 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.

[49] Kim KP, Hong YS, Lee JL, Bae KS, Kim HS, Shin JG, et al. A phase i study of UGT1A1 *28/*6 genotype-directed dosing of irinotecan (CPT-11) in Korean patients with metastatic colorectal cancer receiving FOLFIRI. Oncol 2015. https://doi.org/10.1159/000368674.

[50] 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. https://doi.org/10.1200/JCO.2009.23.6125.

[51] Toffoli G, Sharma MR, Marangon E, Posocco B, Gray E, Mai Q, et al. Genotype-guided dosing study of FOLFIRI plus bevacizumab in patients with metastatic colorectal cancer. Clin Cancer Res 2017. https://doi.org/10.1158/1078-0432.CCR-16-1012.

[52] 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. https://doi.org/10.1053/j.seminoncol.2017.02.007.

[53] Xu R, Muro K, Kim TW, Park YS, Wang W, Han S-W, et al. Impact of UGT1A1 genotype on the efficacy and safety of irinotecan-based chemotherapy in metastatic colorectal cancer (mCRC): A preplanned analysis of the phase III AXEPT trial. Ann Oncol 2018. https://doi.org/10.1093/annonc/mdy431.002.

[54] 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 UGT1A 1 genotype. Br J Cancer 2019. https://doi.org/10.1038/s41416-018-0348-7.

[55] FDA. Camptosar: full prescribing information n.d. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020571s048lbl.pdf (accessed May 8, 2020).

[56] PMDA. Irinotecan: package insert n.d. https://www.pharmgkb.org/chemical/PA450085/labelAnnotation/PA166123526 (accessed May 8, 2020).

[57] HCSC. Irinotecan: product monograph n.d. https://www.pharmgkb.org/chemical/PA450085/labelAnnotation/PA166127683 (accessed May 8, 2020).

[58] Etienne-Grimaldi MC, Boyer JC, Thomas F, Quaranta S, Picard N, Loriot MA, et al. UGT1A1 genotype and irinotecan therapy: General review and implementation in routine practice. Fundam Clin Pharmacol 2015;29:219–37. https://doi.org/10.1111/fcp.12117.

[59] KNMP-DPWG. UGT1A1: irinotecan 2018. https://www.g-standaard.nl/risicoanalyse/B0001694.PDF (accessed May 8, 2020).

[60] CBG-MEB. Campto: SPC n.d. https://www.geneesmiddeleninformatiebank.nl/smpc/h22820_smpc.pdf (accessed May 8, 2020).

[61] Clinical Pharmacogenetics Implementation Consortium (CPIC) 2020. https://cpicpgx.org/genes-drugs/ (accessed May 8, 2020).

[62] 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. https://doi.org/10.1002/cncr.24428.

[63] 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. https://doi.org/10.2217/14622416.9.5.539.

[64] 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. https://doi.org/10.3109/0284186X.2015.1053983.

[65] Wei X, Cai J, Sun H, Li N, Xu C, Zhang G, et al. Cost-effectiveness analysis of UGT1A1*6/*28 genotyping for preventing FOLFIRI-induced severe neutropenia in Chinese colorectal cancer patients. Pharmacogenomics 2019. https://doi.org/10.2217/pgs-2018-0138.

[66] 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 genotype. Clin Pharmacol Ther 2017.

[67] Toffoli G, Innocenti F, Polesel J, De Mattia E, Sartor F, Dalle Fratte C, et al. The Genotype for DPYD Risk Variants in Patients With Colorectal Cancer and the Related Toxicity Management Costs in Clinical Practice. Clin Pharmacol Ther 2018. https://doi.org/10.1002/cpt.1257.

[68] 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.

[69] Cecchin E, Innocenti F, D'Andrea M, Corona G, De Mattia E, Biason P, et al. Predictive role of the UGT1A1, UGT1A7, and UGT1A9 genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. J Clin Oncol 2009;27:2457–65. https://doi.org/10.1200/JCO.2008.19.0314.

[70] Di Paolo A, Bocci G, Danesi R, Del Tacca M. Clinical Pharmacokinetics of Irinotecan-Based Chemotherapy in Colorectal Cancer Patients. Curr Clin Pharmacol 2008. https://doi.org/10.2174/157488406778249307.

[71] Hertz DL, Glatz A, Pasternak AL, Lonigro RJ, Vats P, Wu Y-M, et al. Integration of Germline Pharmacogenetics Into a Tumor Sequencing Program. JCO Precis Oncol 2018. https://doi.org/10.1200/po.18.00011.

Supplementary Table S2.1: Overview *UGT1A1* genotype-guided dose-finding studies

Group	Ethnicity	Treatment schedule	Polymorphism	Genotype	n	Standard dose	Recommended dose (MTD)	Relative dose intensity (%)
Toffoli et al. 2010 [50]	Caucasian	q2w combined with 5-FU, leucovorin	*28	WT HE	35 24	180 mg/m^2	370 mg/m^2 310 mg/m^2	206 172
Marcuello et al. 2011 [45]	Caucasian	q2w combined with 5-FU, leucovorin	*28	WT HE HO	42 38 14	180 mg/m^2	390 mg/m^2 340 mg/m^2 130 mg/m^2	217 188 72
Satoh et al. 2011 [22]*	Japanese	q2w monotherapy	*6/*28	HO+*6/*28	21	150 mg/m^2	150 mg/m^2	100
Goetz et al. 2013 [46]**	Caucasian	q3w combined with oxaliplatin, capecitabine	*28	WT HE HO	21 18 11	175 mg/m^2	150 mg/m^2 150 mg/m^2 75 mg/m^2	86 86 43
Kim et al. 2013 [47]	Korean	q3w combined with capecitabine	*6/*28	WT HE HO+*6/*28	23 20 7	240mg/m^2	350 mg/m^2 350 mg/m^2 200 mg/m^2	146 146 83
Innocenti et al. 2014 [48]	Mostly Caucasian	q3w monotherapy	*28	WT HE HO	31 28 9	700 mg	850 mg 700 mg 400 mg	121 100 57
Kim et al. 2015 [49]***	Korean	q2w combined with 5-FU, leucovorin	*6/*28	WT HE HO+*6/*28	19 20 4	180 mg/m^2	300 mg/m^2 270 mg/m^2 150 mg/m^2	167 150 83
Toffoli et al. 2017 [51]	Caucasian	q2w combined with 5-FU, leucovorin, bevacizumab	*28	WT HE	25 23	180 mg/m^2	310 mg/m^2 260 mg/m^2	172 144

* Patients homozygous for the *UGT1A1*28* or *UGT1A1*6* allele can receive irinotecan in a starting dose of 150 mg/m^2, but many required dose reductions or delayed treatment in subsequent cycles. ** Oxaliplatin dose was escalated before irinotecan dose escalation, which might have led to lower MTDs of irinotecan. *** No DLTs were observed for the WT and the HO group at the proposed MTDs, but no further dose escalation was performed. This early stop decision was based on safety concerns based on previous studies and due to poor enrolment in the HO group. HE = heterozygous carrier, HO = homozygous carrier, MTD = maximum tolerable dose, WT = wild type.