

## UGT1A1 POLYMORPHISMS AS A PHARMACOGENETIC MARKERS FOR PREDICTION OF IRINOTECAN-INDUCED TOXICITIES IN METASTATIC COLORECTAL CANCER

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### Summary

This paper aimed to review the current status of UGT1A1 polymorphisms as a pharmacogenetic marker for prediction of irinotecan-induced toxicities in metastatic colorectal cancer. Deficiencies in the activity uridine diphosphate glucuronosyltransferases (UGT) are mostly due to gene polymorphisms and can lead to increased exposure to irinotecan and its active metabolite causing severe, sometimes life-threatening treatment-related toxicities. Although data suggest that UGT1A1 polymorphisms, especially homozygous (UGT1A1\*28/\*28, UGT1A1\*6/\*6) are related to severe irinotecan toxicity and some guidelines highlighted the importance of upfront UGT1A1 genotyping in order to give safer irinotecan dose, UGT1A1 genotyping is currently not being routinely performed in the daily clinical practice. It is important to note that genetic polymorphisms of UGT1A1 show ethnic differences and it is suggested that Caucasian patients should be upfront screened for UGT1A1\*28 and Asian patients for UGT1A1\*6 as these polymorphisms are common genetic variation in these populations. Data regarding the association of UGT1A1 polymorphisms and treatment response and survival are conflicting.

Nevertheless, it is important to think about other genetic variations in the context of chemotherapy-induced toxicities, especially dihydropyrimidine dehydrogenase deficiency (DYPD).

In conclusion, UGT1A1 polymorphisms are pharmacogenetic markers which can be used for stratification of patients who are at higher risk of irinotecan-induced toxicities to allow preventive dose reduction to reduce potential toxicities.

**KEYWORDS:** *uridine diphosphate glucuronosyltransferase, gene polymorphisms, colorectal cancer, irinotecan-related toxicity*

### UGT1A1 POLIMORFIZMI KAO PREDIKTIVNI FARMAKOGENETIČKI BILJEZI IRINOTEKANSKE TOKSIČNOSTI U BOLESNIKA S METASTATSKIM KOLOREKTALNIM KARCINOMOM

#### Sažetak

Cilj ovog rada je bio napraviti pregled trenutnog statusa UGT1A1 polimorfizama kao farmakogenetičkih biljega za predviđanje toksičnosti na irinotekansku kemoterapiju u bolesnika s metastatskim kolorektalnim karcinomom. Nedostaci u aktivnosti uridin-difosfat-glukuronoziltransferaze (UGT) su uglavnom zbog polimorfizama gena i mogu dovesti do povećane izloženosti irinotekanu i njihovom aktivnom metabolitu uzrokujući ozbiljne, ponekad životno ugrožavajuće nus-

pojave. Iako podaci sugeriraju da su UGT1A1 polimorfizmi, posebice homozigoti (UGT1A1\*28/\*28, UGT1A1\*6/\*6), povezani s ozbiljnim irinotekanskim nuspojavama i neke smjernice ističu značaj genotipizacije UGT1A1 prije početka liječenja irinotekanom u svrhu davanja sigurnije doze irinotekana, UGT1A1 genotipizacija se trenutno rutinski ne provodi u kliničkoj praksi.

Važno je naglasiti da UGT1A1 genski polimorfizmi pokazuju etničke razlike te se preporuča da se bijelci testiraju na UGT1A1\*28, a azijati na UGT1A1\*6 s obzirom da su ti polimorfizmi najčeće genske varijacije u tim populacijama. Podatci o povezanosti UGT1A1 polimorfizama i odgovora na terapiju i preživljenje su proturječni. Također je bitno misliti i na druge genske varijacije u kontekstu kemoterapijom-inducirane toksičnosti, posebice nedostatka enzima dihidropirimidin dehidrogenaze.

U zaključku, UGT1A1 polimorfizmi su farmakogenetički biljezi koji bi se mogli koristiti za izdvajanje pacijenata koji su pod većim rizikom za razvijanje irinotekanom-inducirane toksičnosti i omogućiti im preventivno smanjenje doze u svrhu smanjenja potencijalne toksičnosti.

**KLJUČNE RIJEČI:** *uridin-difosfat–glukuronoziltransferaza, genski polimorfizmi, kolorektalni karcinom, irinotekanom izazvane nuspojave*

## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide (1). The overall survival of patients with metastatic CRC has increased to approximately 3 years with current therapy (2). Treatment options for CRC are dependent on the stage of the disease, tumor biology, patients general condition, comorbidities, previous therapy and their wishes. Chemotherapy-induced toxicities are very important factor because they can restrict the clinical application of chemotherapy.

Irinotecan is a topoisomerase 1 inhibitor, it binds to the DNA/topoisomerase I complex during DNA replication, preventing the resealing of single-strand breaks. Irinotecan is a cornerstone chemotherapy agent for the first-line treatment of metastatic colorectal cancer (mCRC) together with 5-fluorouracil (5-FU) and oxaliplatin with the addition of targeted therapy according to NRAS/KRAS/BRAF status; epidermal growth factor receptors (EGFR) inhibitors cetuximab/panitumumab or anti-vascular endothelial growth factor (VEGF) bevacizumab (2,3).

Irinotecan is usually co-administered with infusional 5-fluorouracil/leucovorin (FOLFIRI regimen), with the addition of targeted therapies, as a front line for patients with metastatic colorectal cancer. Irinotecan treatment has an acceptable safety profile in most patients, but up to 35% of patients treated with combination regimens of 5-FU and irinotecan experience clinically relevant treatment-related toxicities, mainly diarrhea, stomatitis and myelosuppression (4,5). The number of clinically relevant treatment-related toxicities increases sig-

nificantly, up to 35-50%, with the intensification of the treatment using triplet regimen (FOLFOXIRI; 5-FU, oxaliplatin and irinotecan) (6,7).

Irinotecan is converted into its active form 7-ethyl-10-hydroxycamptothecin (SN-38) by a carboxylsterase and inactivated through uridine diphosphate glucuronosyltransferase (UGT1A1). Several isoforms of UDP-glucuronosyltransferase (UGT) enzyme are responsible for hepatic bilirubin glucuronidation (8). The glucuronidation of an active form of irinotecan (SN-38) is catalyzed by UGT1A1, UGT1A3, UGT1A6 and UGT1A9, but UGT1A1 has the highest activity. Thus, reduced UGT1A1 expression can affect on irinotecan metabolism and lead to increased risk of irinotecan associated toxicity (8).

Genetic variations within the UGT1A1 gene, known as polymorphisms, can lead to decreased enzyme activity and are associated with a higher risk of severe toxicity with irinotecan, such as neutropenia and diarrhea. UGT1A1\*1 is a common variation with six TA repeats in promoter region while the seven-repeat variant UGT1A1\*28 is responsible for a dramatically reduced expression of UGT1A1 causing an increase in adverse events due to poor metabolism of the SN38 active metabolite of irinotecan (9,10). UGT1A1\*28 homozygote genotype was found in less than 10% of the Croatian population (11). UGT1A1\*6, a nonsynonymous single nucleotide polymorphism (SNP) in exon 1, was frequently found in an Asian population (12).

### Clinical significance of UGT1A1 gene polymorphisms

Clinically relevant, dose-limiting irinotecan-related toxicities include myelosuppression diarrhea and dehydration (13). Several meta-analy-

ses were conducted to assess the association of UGT1A1 gene polymorphisms and the occurrence of irinotecan-related severe neutropenia and diarrhea. Majority of them included other tumor sites beside CRC (14-19). Other limitations were the inclusion of patients who were treated with different chemotherapy protocols, different doses of irinotecan, different polymorphism detection methods were used across studies (14-20). The most relevant meta-analysis from Liu et al. assessing the association of UGT1A1 gene polymorphisms and irinotecan-induced neutropenia and diarrhea included only patients with CRC. It showed more than fourfold (OR 4.79, 95% CI 3.28-7.01;  $P < 0.00001$ ) increase in the risk of neutropenia for UGT1A1\*1/\*28 genotype, and twofold (OR 1.90, 95% CI: 1.44-2.51;  $P < 0.00001$ ) increase in the risk of neutropenia for UGT1A1\*1/\*28 genotype, compared to UGT1A1\*1/\*1. The risk of diarrhea was around twofold increased (OR 1.84, 95% CI 1.24–2.72;  $P < 0.002$ ) for UGT1A1\*28 homozygous patients compared to UGT1A1\*1/\*1 (20).

Conflicting data were published regarding the association of UGT1A1\*28 polymorphisms and response to chemotherapy and survival outcomes (21-26). Recent Liu et al meta-analysis showed that UGT1A1\*28 polymorphisms were associated with a higher response among patients with metastatic colorectal cancer (OR 1.24, 95%CI 1.05–1.48) compared to UGT1A1\*1/\*1 (19).

A dose of irinotecan seems to be relevant for irinotecan-related toxicities. Metaanalysis from Hu et al. showed no association between UGT1A1\*28 genotype and severe diarrhea treated with low doses of irinotecan ( $< 125$  mg/m<sup>2</sup>) (RR 0.65, 95% CI 0.27-1.58), while the risk of severe diarrhea was significantly higher for patients with UGT1A1\*28 genotype treated with medium or high irinotecan doses (OR 1.79, 95% CI 1.08–2.97 – medium dose, OR 2.32 95% CI 1.25-4.28 – high dose) (15). In subgroup meta-analysis of Liu et al. also showed higher incidence of diarrhoea in UGT1A1\*28/\*28 patients treated with higher dose of irinotecan ( $> 150$  mg/m<sup>2</sup>) (OR=2.37, 95% CI: 1.39-4.04;  $P = 0.002$ ) while patients with UGT1A1\*1/\*28 genotype had slightly increased risk (OR 1.39, 95% CI: 0.97–1.98;  $P = 0.07$ ) of borderline significance (20).

Hoskins et al suggested that association between UGT1A1\*28 genotype and neutropenia is dose-dependent and that it had no effect on patients treated with low dose of irinotecan ( $< 150$

mg/m<sup>2</sup>) while on the other hand, Hu et al found that UGT1A1\*28/28\* genotype was associated with an increased risk of neutropenia even at low doses (RR 2.43 – low dose  $< 150$ mg/m<sup>2</sup>, RR 2.00 medium-dose 150-250 mg/m<sup>2</sup>, RR 7.22 high dose  $> 250$ mg/m<sup>2</sup>) (16, 18).

In a trial designed to define the maximum tolerated dose according to UGT1A1 genotype maximum tolerable dose in patients with UGT1A1\*28/\*28 genotype was found to be 30% lower than the standard dose of 180 mg/m<sup>2</sup> (27).

There are concerns that reduced dose will not be equally effective, and an open question whether patients with UGT1A1\*28/\*28 genotype should be treated with other chemotherapeutic regimens which would be more suitable and effective for them (5).

A recent study from Fujii et al. showed that incidence rates of hematological as well as non-hematological toxicities were not significantly different among patients with different UGT1A1 polymorphisms when the initial dose of irinotecan was reduced by 20% in patients with homozygous mutations. The study also showed that the reduction in the initial dose of irinotecan by 20% in mCRC patients with homozygous mutations in UGT1A1 genes did not impair efficacy of chemotherapy containing irinotecan (28).

#### **Current status of UGT1A1 gene polymorphism screening**

Genetic polymorphisms of UGT1A1 show ethnic differences. It is reported that UGT1A1\*28 occurs with a frequency of 0.26–0.31 in Caucasians, 0.42–0.56 in African Americans, and 0.09–0.16 in Asian populations, while UGT1A1\*6 has allele frequencies of around 0,2 for Asian population (29-31).

Several meta-analyses in Asian-only patients showed a lesser association between UGT1A1\*28 compared to UGT1A1\*6 genotype and irinotecan-induced neutropenia, suggesting that UGT1A1\*6 genotype could be a good predictor of irinotecan-induced toxicity in this population (16,17). It is recommended that Caucasian patients should be upfront screened for UGT1A1\*28 and Asian patients for UGT1A1\*6 as these polymorphisms are common genetic variation in these populations (32). Both of these polymorphisms can result in approximately 70% reduction of UGT1A1 activity in carriers causing increased systemic exposure to

irinotecan and SN-38 in homozygous patients for these variants and increase the risk of irinotecan-related toxicities (32).

Current FDA recommendation regarding dose reduction in patients homozygous for the UGT1A1\*28 allele receiving irinotecan is not precise. The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) recommends starting with 30% reduced dose for homozygous carriers of the UGT1A1\*28 allele with the possibility to increase the dose if well tolerated, guided by the neutrophil count. Also stating that no action is needed for heterozygous carriers of the UGT1A1\*28 allele. French National Network of Pharmacogenetics (RNPGx) has dose-dependent recommendation stating that presence of the UGT1A1\*28 allele is not a major risk factor for patients treated with lower doses of irinotecan (<180 mg/m<sup>2</sup>), at medium doses (180–230 mg/m<sup>2</sup>) 25-30% dose reduction is recommended for patients homozygous for the UGT1A1\*28 allele, while the administration of irinotecan at this higher dose (>230 mg/m<sup>2</sup>) is contraindicated for homozygous for the UGT1A1\*28 allele and leading to discussion of a standard dose depending on the associated risk factors. High dose of irinotecan (240 mg/m<sup>2</sup>) is recommended only for \*1/\*1 patients, or for heterozygous UGT1A1\*28 patients who have no other risk factors and who benefit from intensive surveillance (33-36).

Current NCCN guidelines state that although commercial tests are available to detect the UGT1A1\*28 allele guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on patients who experienced irinotecan toxicity is not recommended, as they will require a dose reduction regardless of the UGT1A1 test result (3). Therefore, the adoption of an upfront UGT1A1\*28 genotyping to increase irinotecan safety in clinical practice is still limited and currently not routinely performed (32).

The patient safety and clinical outcomes could be substantially improved by upfront UGT1A1 screening and UGT1A1- guided dose individualization to predict, diminish and even avoid toxicity to improve the therapeutic effect of irinotecan (5).

The recent cost-effective analysis showed that the costs of the management of irinotecan-related toxicity are significantly higher in patients

carrying either a \*28/\*28 or a \*1/\*28, as compared to \*1/\*1 genotype. The cost of all toxicities management per patient increased 1.4 folds for \*1/\*28 carriers in comparison to \*1/\*1, and 6-fold for the \*28/\*28 patients (37).

#### Other pharmacogenetic markers for CRC chemotherapy-related toxicity

Irinotecan has a toxicity profile which overlaps with those of fluoropyrimidines (5-fluorouracil and capecitabine). Dihydropyrimidine dehydrogenase (DYPD) gene encodes for the enzyme dihydropyrimidine dehydrogenase (DPD), which is important for the metabolism of fluoropyrimidines and de-activates more than 80% of administered fluoropyrimidine. Factors such as age, race, comorbidities, and concomitant therapies also influence metabolism (38).

Reduced or absent activity of this enzyme in DYPD deficient patients can result in severe and sometimes fatal toxicity; severe and prolonged pancytopenia, sometimes associated with sepsis, serious gastrointestinal toxicity with refractory diarrhea and dehydration, severe mucositis and severe skin changes (39-41). There are numerous genetic variants in DPYD, but four DPYD variants causing decreased function were shown to be important for patients treated with fluoropyrimidines: c.1905+1G>A (rs3918290, also known as DPYD\*2A, DPYD:IVS14 + 1G>A), c.1679T>G (rs55886062, DPYD \*13, p.I560S), c.2846A>T (rs67376798, p.D949V), and c.1129–5923C>G (rs75017182, HapB3). Among those c.1905+1G>A and c.1679T>G have the most deleterious impact on DPD activity (40).

Around ~7% of Europeans carry at least one decreased function DPYD variant. The most common is c.1129–5923C>G decreased function DPYD variant with carrier frequencies of 4.1–4.8%, while carrier frequency for c.1905+1G>A is much rarer, 1–1.2% (40).

Currently upfront DPYD genotyping remains controversial, as it is the case with UGT1A1 genotyping.

Furthermore, other genetic variation including the carboxylesterase 1 (CES1) gene, the multidrug resistance-associated protein 2 (MRP2) gene, and organic anion-transporter family, member 1B1 (OATP1B1; SLCO1B1) gene, are suggested to be associated with interindividual variability in

the pharmacokinetics and subsequently with toxicity to irinotecan (12).

## CONCLUSION

Irinotecan is a crucial component of chemotherapy regimens for the treatment of metastatic colorectal cancer. UGT1A1 polymorphisms can cause a reduction in enzymatic activity that can induce severe, sometimes life-threatening toxicities with a standard dose of irinotecan. Therefore, using UGT1A1 polymorphisms would be beneficial with the rationale to personalize the dosing of irinotecan according to UGT1A1 genotype status to reduce toxicities and optimize treatment effect, although its use as an upfront screening to increase irinotecan safety is still limited and currently not routinely performed in the daily clinical practice.

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