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ORIGINAL RESEARCH

The association between *UGT1A1* polymorphisms and treatment toxicities of liposomal irinotecan

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Background: Initial dose adjustment is recommended for patients with known *UGT1A1*28* homozygosity for both conventional irinotecan and liposomal irinotecan (nal-IRI). A recent population pharmacokinetic (PK) study showed that Asian patients had a lower prevalence of *UGT1A1*28* homozygosity but a significantly higher maximum blood concentration of SN-38 (SN-38 Cmax) and a higher incidence of grade ≥3 neutropenia after nal-IRI administration than Caucasian patients. The current study investigated the association of *UGT1A1* polymorphisms, including the Asian prevalent *UGT1A1*6*, PK and toxicities of nal-IRI-based therapy in the Asian population.

Patients and methods: A total of 162 patients with nal-IRI-based therapy and available *UGT1A1*6* and *UGT1A1*28* genotyping were included, with 82 Asian patients from six previous phase I or II studies of nal-IRI (cohort 1) and another 80 patients with nal-IRI + 5-fluorouracil/leucovorin every 2 weeks as real-world practice in a single institute in Taiwan (cohort 2).

Results: The frequency of *UGT1A1*6* or *UGT1A1*28* homozygosity/compound heterozygosity was 9.3%, with *UGT1A1*6/*6* in 2.5%, *UGT1A1*28/*28* in 1.9% and *UGT1A1*6/*28* in 4.9%. Among the 53 patients in cohort 1 with available PK data, all 7 patients with homozygosity/compound heterozygosity harbored *UGT1A1*6* and had a significantly higher level of median dose-normalized area under the concentration—time curve (AUC) and Cmax of SN-38 than those with single heterozygosity/wild type. Of the entire study population, the incidence of grade ≥3 neutropenia and diarrhea was significantly higher in patients with homozygosity/compound heterozygosity than in those with single heterozygosity/wild type, 73.3% versus 38.1% ($P = 0.012$, Fisher's exact test) and 33.3% versus 9.5% ($P = 0.018$, Fisher's exact test), respectively.

Conclusion: The results suggest that the recommendation of a lower starting dose of nal-IRI for patients with *UGT1A1*28* homozygosity should be extended to include patients with *UGT1A1*6* homozygosity/compound heterozygosity.

Key words: *UGT1A1*6*, nal-IRI, neutropenia, diarrhea, Asian

INTRODUCTION

Liposomal irinotecan (nal-IRI) is the first and also, to date, the only approved agent for gemcitabine-containing treatment failed advanced pancreatic cancer after the pivotal NAPOLI-1 trial.[1] Nal-IRI is a new formulation of irinotecan hydrochloride, which encapsulates irinotecan in pegylated liposomes and therefore prevents irinotecan from circulating protein binding and premature metabolism, resulting in different pharmacokinetic (PK) properties (lower peak concentration and prolonged half-life).[2,3] After intravenous infusion administration, irinotecan released from nal-IRI is converted to SN-38, which is 100-1000 times more active than irinotecan. SN-38 is then inactivated and detoxified into its

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Table 1. Summary of patient enrollment

	Study	All patients in the study			Patients with PGx	
		Total accrual	Asian	Caucasian	Asian	Caucasian
Cohort 1	PEP0201, phase I, solid tumor Nal-IRI, every 3 weeks Jan. 2005-Aug. 2005	11	11	0	3	0
	PEP0202, phase I, cervical cancer Nal-IRI + cisplatin, every 3 weeks Jan. 2006 — Mar. 2008	6	6	0	6	0
	PEP0203, phase I, solid tumor Nal-IRI + HDFL, every 3 weeks Mar. 2006 — Aug. 2008	16	16	0	16	0
	PEP0206, phase II, gastric cancer Nal-IRI arm, every 3 weeks Jan. 2008 — Jun. 2010	45	21	24	16	20
	PEP0208, phase II, pancreatic cancer Nal-IRI, every 3 weeks Mar. 2009 — Sep. 2010	40	25	15	23	5
	PIST-CRC-01, phase II, colorectal cancer Nal-IRI, every 2 weeks June 2009-May 2012	18	18	0	18	0
	Sum	136	97	39	82	25
Cohort 2	NCKUH	80	80	0	80	0
Patients enrolled in final analysis		—	—	—	162	—

HDFL, high-dose 5-fluorouracil/leucovorin; nal-IRI, liposomal irinotecan; NCKUH, National Cheng Kung University Hospital; PGx, pharmacogenomics.

inactive form, SN-38 glucuronide, by the uridine diphosphate (UDP)-glucuronosyltransferase 1 (UGT1) encoded by the *UGT1A1* gene.[4] Individuals with reduced UGT1 enzyme activity have been known to suffer from more significant adverse events than those with normal UGT1 activity.

Of the reported *UGT1A1* gene polymorphisms, *UGT1A1*28* (TA_7), which contains seven, commonly six, TA repeats in the TATA box of *UGT1A1* promoter region, and *UGT1A1*6* (c.211G>A, p.Gly71Arg) are the most commonly described *UGT1A1* polymorphisms that are associated with decreased UGT activity and increased incidence of adverse events related to irinotecan, mainly neutropenia and diarrhea.[4,5] The distributions of *UGT1A1* polymorphisms among Caucasians and Asians are very different that the *UGT1A1*28* was more common in Caucasians (allele frequency 30.4%-38.8%) than in Asians (allele frequency 6.6%-16.7%), while *UGT1A1*6* was more common in Asians (15.7%-31%) but extremely rare in Caucasians (0.7%).[6-12]

In previous population PK study, patients with *UGT1A1*28* homozygosity had similar SN-38 peak concentration (Cmax) as compared to patients with single heterozygosity and wild type.[13,14] This phenomenon was possibly attributed to the slow release of irinotecan after nal-IRI administration, which allowed the adequate metabolism of SN-38, even in patients with *UGT1A1*28* homozygosity. On the other hand, ethnicity was the most significant predictive factor for the Cmax of both total irinotecan and SN-38 following the administration of nal-IRI and Asian patients experienced more neutropenia and less diarrhea than Caucasian patients as shown in the NAPOLI-1 study. Since *UGT1A1*6* is more prevalent in the Asian population, the association among *UGT1A1*6*, PK of nal-IRI and toxicities merits further investigation. However, *UGT1A1*6* was not tested in the NAPOLI-1 study and thus not included into the analysis of previous population PK study.[13] Herein, we collect the pharmacogenetics and PK profile of six phase I or II clinical trials (cohort 1) and real-world data from a single institute (cohort 2) to explore the association between *UGT1A1* polymorphisms and nal-IRI treatment toxicities in the Asian population.

PATIENTS AND METHODS

Patients

Between January 2005 and May 2012, a total of 136 patients were enrolled in six phase I or II nal-IRI clinical studies (PEP0201, PEP0202, PEP0203, PEP0206, PEP0208 and PIST-CRC-01) at doses from 60 to 180 mg/m^2 every 2 or 3 weeks as monotherapy or combination therapy. Among 107 patients with available pharmacogenetic profiling, 82 Asian patients were included as cohort 1 (Table 1). All patients had given written informed consent before the enrollment in each clinical trial and pharmacogenetic study. Another 80 patients who received nal-IRI + 5-fluorouracil (5-FU)/leucovorin (LV) as daily practice at National Cheng Kung University Hospital, Taiwan, were included as cohort 2. All of them signed informed consent for the collection of genomic DNA for genetic analysis in a prospective case-control study titled 'Environmental and Genetic Epidemiology and Prognostic Study of Pancreatic Cancer' that was begun in 2013 (National Cheng Kung University Hospital approval number B-BR-102-070). The study was approved by the Institutional Review Board and followed the Declaration of Helsinki and Good Clinical Practice guidelines.

Assessment

Patient demographics and clinical characteristics including sex, age, tumor type, severity of diarrhea, severity of

Table 2. Distribution of *UGT1A1* polymorphism by patient cohort

	Study	Patient number	Homozygosity		Compound heterozygosity	Single heterozygosity		Wild type in *6 and *28
			*6/*6	*28/*28	*6/*28	*1/*6	*1/*28	*1/*1
Cohort 1	PEP0201	3	0	0	1	0	0	2
	PEP0202	6	1	0	0	0	0	5
	PEP0203	16	0	0	1	4	1	10
	PEP0206	16	1	0	1	4	1	10
	PEP0208	23	0	0	0	2	3	18
	PIST-CRC-01	18	0	0	3	5	1	8
	Sum (% in cohort 1)	82	2 (2.4)	0 (0)	6 (7.3)	15 (18.3)	6 (7.3)	53 (64.6)
Cohort 2	NCKUH, *n* (%)	80	2 (2.5)	3 (3.8)	2 (2.5)	15 (18.8)	15 (18.8)	43 (53.8)
	Sum (% in Asian)	162	4 (2.5)	3 (1.9)	8 (4.9)	30 (18.5)	21 (13.0)	96 (59.3)

neutropenia, dosage of nal-IRI and tumor response of cohort 1 were obtained from the clinical trial datasets (provided by PharmaEngine). Data from cohort 2 were retrospectively manually extracted from the electronic medical record. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and the tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Pharmacokinetics and pharmacogenetics

For cohort 1, serial blood samples were obtained for PK profiling during the first course of nal-IRI administration at proper time point as defined by each study protocol.[2,3,15,16] PK parameters including area under the concentration–time curve from time zero to the last blood sampling time point ($AUC_{0\rightarrow t}$) and the Cmax of total irinotecan and SN-38 were obtained and calculated in 53 Asian patients. Genomic DNA was isolated from buffy coat of peripheral blood for analysis of *UGT1A1* polymorphism in 82 Asian and 25 Caucasian patients. The genotypes of *UGT1A1*6* and *UGT1A1*28* were determined by direct sequencing or TaqMan allelic discrimination assay as described in the protocol.[2,3,15,16]

For cohort 2, genomic DNA was extracted from peripheral blood mononuclear cells. Target-specific primer pairs were designed to cover the coding regions of *UGT1A1*6* and *UGT1A1*28*. PCR was carried out using a BioRad T100™ thermal cycler (BioRad Laboratories, Inc., Hercules, CA). Subsequently, the amplicon in each sample pool was subjected to another PCR step to tag the PCR products with different barcodes and Illumina sequence-specific adapters. The barcoded PCR products were pooled and submitted for next-generation resequencing on an Illumina MiniSeq platform. A total of 2 × 150 bp paired-end runs of Illumina MiniSeq (Illumina, Inc., San Diego, CA) were carried out according to the manufacturer's protocol.

Statistical analysis

The normality of each variable was checked using the Kolmogorov–Smirnov test. Chi-square test with Yates' continuity correction was applied for the evaluation of Hardy–Weinberg equilibrium. Fisher's exact test was used to compare the count data between groups. The Wilcoxon rank sum test and Kruskal–Wallis test were used to compare continuous variables between groups. All variables with $P < 0.05$ were considered statistically significant. All statistical analyses were carried out with R version 4.0 (R Core Team, Vienna, Austria).

RESULTS

Pharmacogenetics

The allele frequencies of *UGT1A1*6* (G>A) and *UGT1A1*28* (TA_7) variants for the entire cohort were 0.142 and 0.108, respectively, and the distribution was consistent with the Hardy–Weinberg equilibrium ($P > 0.1$) in population genetics (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100746). The distributions of *UGT1A1* polymorphisms for cohort 1 and cohort 2 are summarized in Table 2. The frequencies of homozygosity/compound heterozygosity (*UGT1A1*6/*6, UGT1A1*28/*28 or UGT1A1*6/*28*) in cohort 1 and cohort 2 were 9.7% and 8.8%, respectively, and 9.3% for the entire study population. The distributions of *UGT1A1* polymorphisms in 25 Caucasian patients from the PEP0206 and PEP0208 studies are listed in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100746.

Adverse events

Of the entire study population, patients with homozygosity/compound heterozygosity had a significantly higher incidence of grade ≥3 neutropenia than patients with single heterozygosity or wild type, 73.3% versus 38.1% ($P = 0.012$, Fisher's exact test), as did for grade ≥3 diarrhea 33.3% versus 9.5% ($P = 0.018$, Fisher's exact test) (Figure 1 and Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100746). The incidence of grade ≥3 neutropenia was consistent between cohort 1 and cohort 2 and was observed at different dose levels of nal-IRI, while grade ≥3 diarrhea mostly occurred in cohort 1 patients with initial nal-IRI dose ≥80 mg/m^2 and less common in cohort 2 patients (Figure 2).

In cohort 1, the incidence of neutropenia grade ≥3 was significantly higher in Asian patients than in Caucasian patients who were included in the PEP0206 and PEP0208

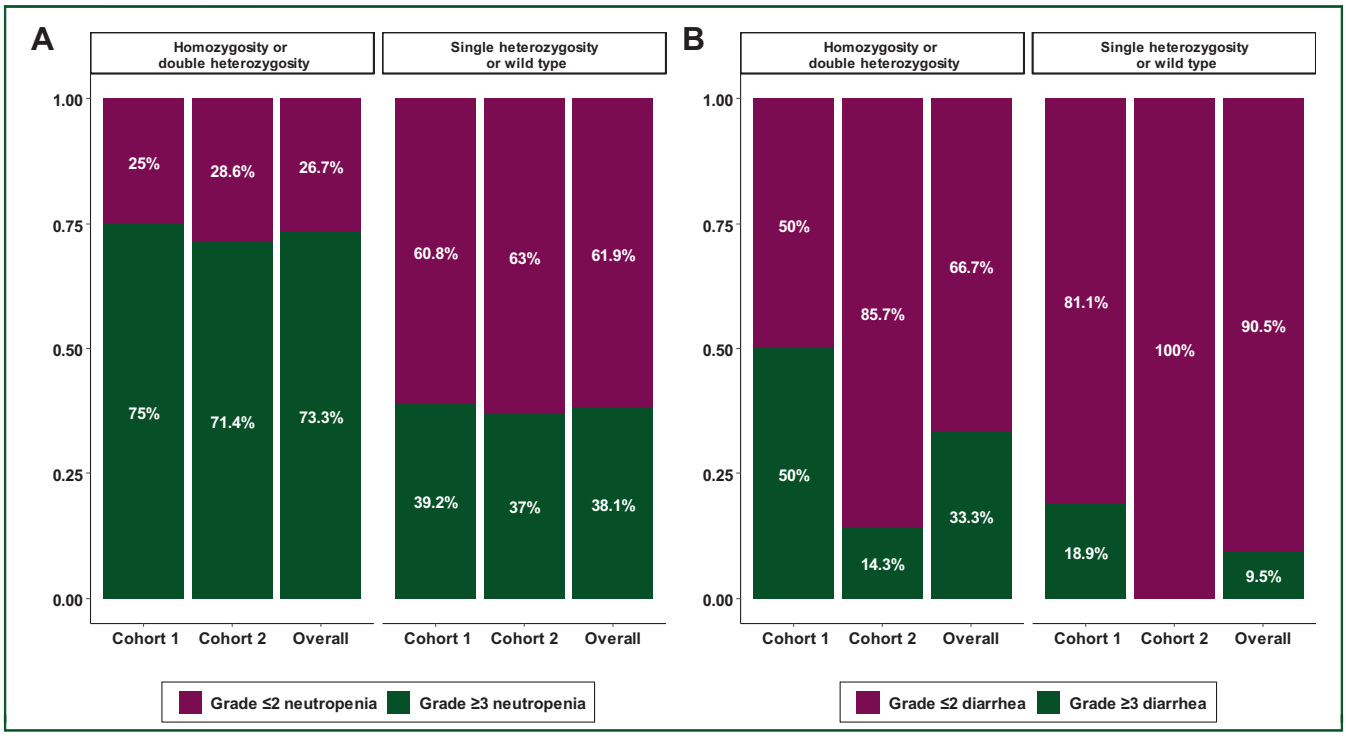

Figure 1. Incidence of grade ≥3 toxicities in each genotype. The incidence of neutropenia (A) and diarrhea (B) in cohort 1, cohort 2 and entire study population is depicted.

studies, 41.4% (67/162) versus 8% (2/25), respectively ($P < 0.001$); the trend was observed in all genotypes. Diarrhea grade ≥3 was numerically lower in Asian patients than in Caucasian patients, 11.7% versus 28.0%, respectively ($P = 0.055$) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100746).

Pharmacokinetics

The PK profile of nal-IRI was available in 53 Asian patients in cohort 1. Since the starting dose was different, the AUC and Cmax were normalized by the starting dose. The median dose-normalized AUC of SN-38 ($SN\text{-}38_{AUC}$) was significantly higher in patients with homozygosity/compound heterozygosity compared to those with single heterozygosity and wild type (8.27 versus 3.15 ng·h/ml/mg, respectively, $P = 0.022$) (Figure 3A), while the median dose-normalized AUC of total irinotecan ($tIRI_{AUC}$) was similar, 7.09 and 8.72 μg·h/ml, respectively ($P = 0.83$) (Figure 3B). The median dose-normalized Cmax of SN-38 ($SN\text{-}38_{Cmax}$) was also significantly higher in homozygosity/compound heterozygosity than in single heterozygosity and wild type, 0.092 and 0.060 ng/ml/mg, respectively ($P = 0.019$) (Figure 3C); the median dose-normalized total irinotecan Cmax ($tIRI_{Cmax}$) was not significantly different between the two groups, 0.496 and 0.451 μg/ml/mg, respectively ($P = 0.39$) (Figure 3D).

The relationship among PK parameters and grade ≥3 neutropenia or diarrhea in cohort 1 is depicted in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100746. The median dose-normalized $SN\text{-}38_{AUC}$ was significantly higher in patients who experienced grade ≥3 neutropenia and/or diarrhea than in those experiencing grade 0-2, 4.43 versus 3.10 ng·h/ml/mg ($P = 0.02$) and 4.68 versus 3.12 ng·h/ml ($P = 0.041$), respectively (Supplementary Figure S1A and E, available at https://doi.org/10.1016/j.esmoop.2022.100746). The median dose-normalized AUC of total irinotecan ($tIRI_{AUC}$) was also significantly higher in patients with grade ≥3 diarrhea than in those with grade 0-2, 13.0 versus 7.8 μg·h/ml/mg ($P = 0.037$) (Supplementary Figure S1F, available at https://doi.org/10.1016/j.esmoop.2022.100746), but not significantly different in those with neutropenia of grade ≥3, 8.55 versus 8.34 μg·h/ml in grade 0-2 ($P = 0.64$) (Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmoop.2022.100746). On the other hand, both median dose-normalized $SN\text{-}38_{Cmax}$ and $tIRI_{Cmax}$ were similar for patients with grade ≥3 versus grade 0-2 neutropenia or diarrhea (Supplementary Figure S1C, D, G and H, available at https://doi.org/10.1016/j.esmoop.2022.100746).

DISCUSSION

This is the first study to emphasize the impact of *UGT1A1*6* variant on the PK and adverse events after nal-IRI treatment in the Asian population. The allele frequencies of *UGT1A1*6* (0.142) and *UGT1A1*28* (0.108) variants are in the range of reports in the Asian populations.[6-12] The incidence of homozygosity/compound heterozygosity and their association with high incidence of grade ≥3 neutropenia after nal-IRI-containing treatment in the current study were consistent with those observed in the Japanese bridging phase II study, 9.3% (15/162) versus 8.9% (7/79) and 73.3% (11/15) versus 100% (3/3), respectively.[17] In addition, our PK subgroup

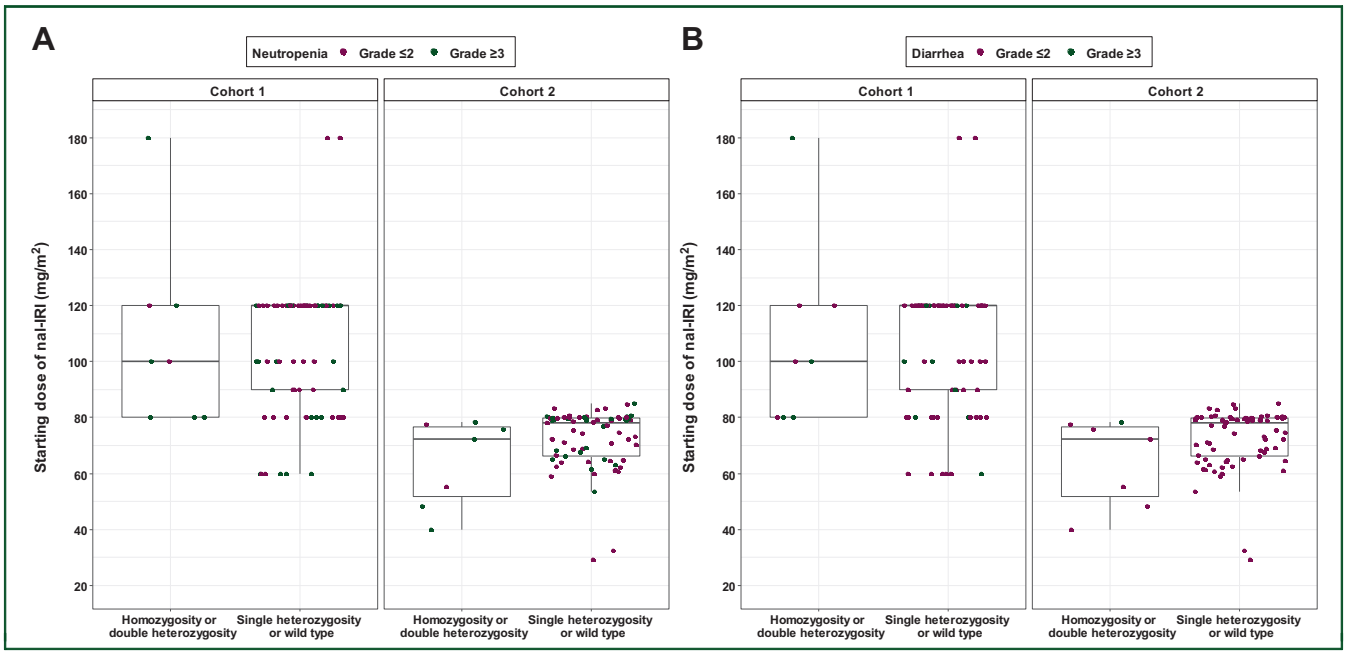

Figure 2. Starting dose and treatment toxicities. Distribution of grade ≥3 neutropenia (A) and diarrhea (B) at different doses in each genotype. Median (line inside box), 25th and 75th percentiles (lower and upper box boundaries) of initial liposomal irinotecan (nal-IRI) dose in patients with homozygosity or compound heterozygosity (*UGT1A1*6/*6* or *UGT1A1*6/*28*), single heterozygosity (*UGT1A1*1/*6* or *UGT1A1*1/*28*) or wild type are presented. Each dot represents one patient.

analysis showed that Asian patients with grade ≥3 neutropenia had a significantly higher dose-normalized SN-38_{AUC} ($P = 0.02$, Supplementary Figure S1A, available at https://doi.org/10.1016/j.esmoop.2022.100746) and SN-38_{Cmax} ($P = 0.041$, Supplementary Figure S1E, available at https://doi.org/10.1016/j.esmoop.2022.100746) than those with grade 0-2 neutropenia. The results were consistent with the previous cross-continental population PK study, which identified SN-38_{Cmax} as a PK parameter associated with grade ≥3 neutropenia.[13] Furthermore, SN-38_{Cmax} was significantly higher in the Asian cohort than in the Caucasian cohort ($P < 0.001$) which may partially explain why Asians experienced more grade ≥3 neutropenia after nal-IRI administration.

The greater impact of *UGT1A1*6* homozygosity and compound heterozygosity than *UGT1A1*28* homozygosity on nal-IRI-related grade ≥3 neutropenia was further supported by two prospective clinical trials.[1,17] With the starting dose at 60 mg/m^2 (25% reduction) of nal-IRI in combination with 5-FU/LV, three of the seven patients with *UGT1A1*28* homozygosity in NAPOLI-1 had nal-IRI dose escalation to standard 80 mg/m^2 in subsequent treatment cycles and another each patient required further dose reduction to 40 mg/m^2 or discontinuation due to grade 3 vomiting,[1] while all the three patients with *UGT1A1*6* homozygosity or compound heterozygosity in the Japanese phase II study experienced grade ≥3 neutrophil count decrease.[17] Furthermore, of the three patients with *UGT1A1*6* homozygosity or compound heterozygosity receiving ≤60 mg/m^2 of nal-IRI starting dose in our cohort 2, grade ≥3 neutropenia occurred in the two patients with *UGT1A1*6* variant (*UGT1A1*6/*6* and *UGT1A1*6/*28* in one each), but not in the one with *UGT1A1*28/*28* genotype (Figure 2A). These findings support the extension of requesting a lower starting dose of nal-IRI for patients with *UGT1A1*28* homozygosity to include Asian patients with *UGT1A1*6* homozygosity/compound heterozygosity, as recommended in the Japanese bridging phase II study protocol and the regulatory approved package insert.[17,18] Further investigation to determine the optimal nal-IRI starting dose, 60 mg/m^2 or lower, for patients with the *UGT1A1*6/*6* or *UGT1A1*6/*28* genotype is warranted.

In the NAPOLI-1 study, the incidence of grade ≥3 diarrhea was closely associated with $tIRI_{Cmax}$, and both were higher in the Caucasian (versus Asian) population and in patients receiving higher dose of nal-IRI (120 mg/m^2 as monotherapy versus 80 mg/m^2 plus 5-FU/LV).[1,13,19] Interestingly, the association between grade ≥3 diarrhea and $tIRI_{Cmax}$ was only observed in the nal-IRI monotherapy group but not in the nal-IRI + 5-FU/LV group in the NAPOLI-1 study which suggested that grade ≥3 diarrhea most likely occur with high-dose nal-IRI (resulting in higher $tIRI_{Cmax}$).[13] The observation was endorsed by the Japanese phase II study and our recent nationwide real-world data analysis that included current cohort 2 patients. In the former study, none of the three patients with *UGT1A1*6/*6* or *UGT1A1*6/*28* genotype and 60 mg/m^2 nal-IRI starting dose experienced grade ≥3 diarrhea, while in the latter study, the incidence of grade ≥3 diarrhea was 2.7% in 473 Taiwanese patients receiving nal-IRI + 5-FU/LV in daily practice with a median nal-IRI starting dose of 65.8 mg/m^2 (interquartile range 57.3-77.8 mg/m^2).[20] In the current study, grade ≥3 diarrhea mainly occurred in Asian patients receiving nal-IRI starting dose of 80-180 mg/m^2 and rarely in those with starting dose <80 mg/m^2 (Figure 2B) even in patients of *UGT1A1*6* homozygosity or compound heterozygosity genotype. These observations suggested that optimal nal-IRI starting dose redcution can effectively

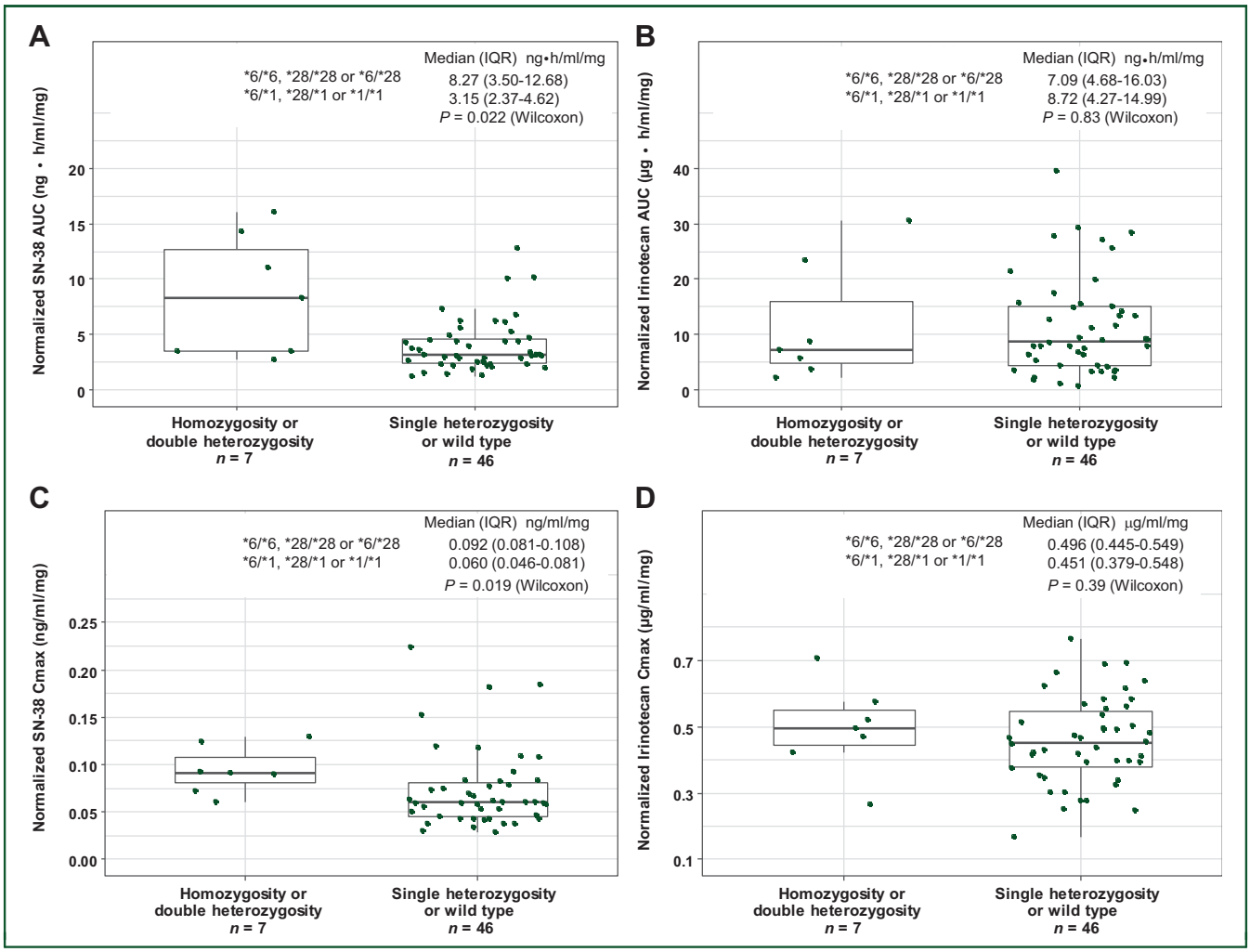

Figure 3. Scatterplot of dose-normalized AUC and Cmax in each genotype. Median (line inside box), 25th and 75th percentiles (lower and upper box boundaries) of SN-38 area under curve (A), total irinotecan area under curve (B), SN-38 peak concentration (C) and total irinotecan peak concentration (D) in patients with homozygous or double heterozygous variants (*UGT1A1*6/*6* or *UGT1A1*6*/*28), single heterozygous variants (*UGT1A1*1/*6* or *UGT1A1*1*/*28) or wild type are presented. Each dot represents one patient. AUC, area under the concentration—time curve.

prevent the occurrence of severe diarrhea even in Asian patients with *UGT1A1*6* homozygosity or compound heterozygosity genotype.

There are some limitations in our study. Firstly, the administered dose and schedule of nal-IRI were different among different trials. Therefore, despite the correction with the administered dose, there was still some bias since PK parameters and toxicities were not linearly correlated with administered dose. Secondly, SN-38/SN-38 glucuronide (SN-38G) ratio, an indicator of UGT1A1 activity, was not available in our study because there was no reliable and validated assay method for SN-38G measurement available in Taiwan at that time. Finally, a variety of *UGT1A1* polymorphisms have been reported to affect the metabolism of irinotecan, but only *UGT1A1*6* and *UGT1A1*28* were included in our study. Therefore, the impact of other variants of *UGT1A1* on PK and toxicities cannot be elucidated from our study. However, considering the low prevalence of other *UGT1A1* polymorphisms, analysis of only major polymorphisms is a more cost-effective strategy and applicable to real-world practice.

Conclusion

Nine percent of Asian patients harboring either *UGT1A1*6* or *UGT1A1*28* homozygosity/compound heterozygosity had a higher incidence of grade $\geq$3 neutropenia under nal-IRI-based treatment. For patients with known *UGT1A1*6* homozygosity/compound heterozygosity, a lower starting dose of nal-IRI should be considered as for patients with *UGT1A1*28* homozygosity.

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DISCLOSURE

YWW was employed by PharmaEngine, Inc. BNS is employed by PharmaEngine, Inc. All other authors have declared no conflicts of interest.

DATA SHARING

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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