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ORIGINAL ARTICLE

UGT1A1 Gene Polymorphism Predicts Irinotecan-Induced Severe Neutropenia and Diarrhea in Chinese Cancer Patients

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SUMMARY

Background: **Irinotecan was widely used in colon cancer and lung cancer, etc., and adverse reactions occur some times. The primary aim of this research is to investigate the association between UGT1A1 gene polymorphisms and irinotecan-related adverse effect in Chinese Han population with a novel kind of gene chip technology.**
Methods: **UGT1A1*6/*28 gene polymorphisms were detected by PCR and gene chip as well as sequencing. The correlation between UGT1A1 gene polymorphisms and severe delayed diarrhea or neutropenia and effect on response rate and progression-free survival were analyzed.**
Results: **A total of 106 patients receiving irinotecan-based regimens and with detected UGT1A1 gene polymorphisms were enrolled in this research. According to our results, no significant differences of severe diarrhea were found in patients with UGT1A1*6 genotypes ($p = 0.608$). However, the incidence of severe diarrhea in patients with TA7/7 genotype (66.7%, 4/6) was significantly higher than that in patients with TA6/7 (31.5%, 6/19) or TA6/6 (1.28%, 1/78) genotypes ($p < 0.001$). The incidence of severe hematologic toxicity in patients with AA (100%, 2/2) was significantly higher than that in patients with GA (33.3%, 7/21) or GG genotype (7.23%, 6/83) ($p = 0.011$).**
Conclusions: **In terms of irinotecan-based regimens in cancers, UGT1A1*6 plays a more vital role in hematologic toxicity ($p = 0.011$) whereas UGT1A1*28 get more involved in diarrhea ($p < 0.001$).**
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INTRODUCTION

Irinotecan (CPT-11) is a semisynthetic camptothecin; chemotherapeutic strategies with irinotecan were applied in various cancers (including metastatic colorectal cancer, lung cancer, gastric cancer, esophageal cancer, etc.) and some have resulted in the desired effects [1]. However, its application in clinical practice is limited because of toxicity such as delayed diarrhea and severe hematologic toxicity [2]. In order to figure out the causes that lead to toxicity we carried out this research work.

As a prodrug that targets topoisomerase I inhibitor, irinotecan is activated by the enzymes CES to 7-ethyl-10-hydroxycamptothecin (SN-38). Accumulation of SN-38

in the human body is an important factor responsible for severe toxicity. The uridine diphosphate glucuronosyltransferase (UGT) family of enzymes glucuronidate SN-38 to inactive SN-38G, so that the toxicity is reduced [3]. UGT1A1 is one of the provital enzymes of the UGT family that catalyze SN38-SN-38G [4]. This means that UGT1A1 variants linked with reduced glucuronidation activity are worthy of study.

Studies showed that the activity of UGT1A1 enzyme was closely related to the UGT1A1 gene polymorphisms, especially UGT1A1*6 and UGT1A1*28 [2,4]. The change of TA repeats in the TATA box of the UGT1A1 promoter caused UGT1A1*28 polymorphism, resulting in three genotypes: TA6/TA6, TA6/TA7 (heterozygosity), and TA7/TA7 (homozygosity). With the increase in the number of TA repeats, the expression of UGT1A1 will decrease, which leads to the excessive accumulation of SN-38 and then results in CPT-11-related toxicity. UGT1A1*6 polymorphism, characterized by a single-nucleotide substitution in exon 1 of UGT1A1 (211G.A; GG, GA, and AA genotypes), occurred at a higher frequency in Asians. Researchers also found that UGT1A1*6 polymorphism was associated with irinotecan-related diarrhea and neutropenia in Asians, especially neutropenia.

Although many studies had been conducted to investigate the associations between UGT1A1*28/*6 polymorphisms and irinotecan toxicity, the conclusions were still controversial [5,6]. Additionally, the frequency of adverse effects that are induced by irinotecan were reported to be higher in Europeans than in Asians. This maybe the result of the different distribution of gene polymorphism of UGT1A1*6/*28 in races. There have been no reports about the relationship between gene polymorphism and irinotecan-related efficacy and adverse effects as yet. Meanwhile, a reliable, fast, accurate, and normalized method is also needed to prepare for future clinical detection of UGT1A1*/*28. With this in mind, we conducted this research.

At present, sequencing is the main technique for detecting gene polymorphism, but it is not yet practical in clinical use. The gene chip technology that used in this study was the first approved technique in China for clinical detection. We applied the novel genotyping technique developed by Shanghai Baio R&D department for detecting UGT1A1*6&*28 polymorphism and verified its accuracy by sequencing, preliminarily exploring this newer technique for UGT1A1 polymorphism detection in future clinical application. At the same time, we collected information of cancer patients that received irinotecan treatment and analyzed the correlation of UGT1A1*6&*28 polymorphisms with CPT-11 induced toxicity, especially delayed diarrhea and hematologic toxicity.

MATERIALS AND METHODS

Patients

A total of 106 patients with gastrointestinal cancer or lung cancer that was treated with irinotecan at the Oncology Department of the First Affiliated Hospital of Nanchang University from June 2012 to December 2014 were retrospectively included in this study. All patients gave written informed consent for their peripheral blood to be used for research. The peripheral blood was drawn prior to chemotherapy and stored at -80°C until analysis. All patients received irinotecan-containing chemotherapy, with irinotecan-induced toxicities of delayed onset diarrhea and neutropenia being recorded in detail. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University and was performed according to the Declaration of Helsinki principles.

Treatment, response evaluation, and toxicity assessments

Before irinotecan-containing chemotherapy, an adequate bone marrow function, hepatic and renal function, and performance status of each patient were ensured. Irinotecan-containing chemotherapy was given as first-line treatment in 68 patients, second-line treatment in 38 patients. The chemotherapy regimens and dose of irinotecan in this study contained FOLFIRI (irinotecan 180 mg/m^2), irinotecan alone or plus cisplatin (irinotecan 90 mg/m^2), and irinotecan plus capecitabine (irinotecan 180 mg/m^2). Each patient received irinotecan containing chemotherapy at least once, and complete blood counts were performed after each administration of irinotecan or before the initiation of next use. Clinical response was evaluated every three cycles by computed tomography (CT) according to the response evaluation criteria in solid tumors (RECIST). Patients were categorized by complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Toxicity was evaluated according to NCI-CTC 3.0 criteria (National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0). Grade III or IV diarrhea and neutropenia were defined as severe toxicity.

DNA preparation and genotyping of UGT1A1 by PCR- gene chip hybridization

Genomic DNAs were extracted from peripheral blood using Blood DNA Extraction Kit (Baio, Shanghai, China). DNA fragments aligned, respectively, with TATA box of UGT1A1 promoter and exon 1 of UGT1A1 were amplified by PCR using primers (forward: 5'-CTCTG AAAGTGAACTCCCTGC-3'; reverse: 5'-AGGAAGG AAAGGGTCCGTCA-3'). Gene chip technology is in accordance with the protocol provided by the manufacturer (Baio, Shanghai, China). Each genotype was confirmed by sequencing (Invitrogen, Shanghai, China).

Table 1. Genotyping of UGT1A1 in cancer patients.

Genotyping		No. of patients	%
UGT1A1*6	GG	83	78.30%
	GA	21	19.80%
	AA	2	1.89%
UGT1A1*28	TA6/6	81	76.40%
	TA6/7	19	17.90%
	TA7/7	6	5.66%
UGT1A1*6&*28	GG&TA6/6	62	58.50%
	GG&TA6/7	15	14.10%
	GG&TA7/7	6	5.66%
	GA&TA6/6	17	16%
	GA&TA6/7	4	3.77%
	GA&TA7/7	0	0
	AA&TA6/6	2	1.89%
	AA&TA6/7	0	0
	AA&TA7/7	0	0

Table 2. Prevalence of diarrhea and hematologic toxicity in cancer patients.

Grade of diarrhea				
0	I	II	III	IV
87 (82.1%)	4 (3.77%)	4 (3.77%)	9 (8.49%)	2 (1.88%)
Grade of hematologic toxicity				
0	I	II	III	IV
30 (28.3%)	30 (28.3%)	31 (29.24%)	11 (10.78%)	4 (3.77%)

Statistical analysis

Statistical software SPSS 22.0 (SPSS Inc., Chicago, IL, USA) with Fisher's exact test and Student's *t*-test was used to analyze the relationship between genotyping and irinotecan-induced toxicity. All statistical analyses were two-sided tests, and $p < 0.05$ was considered to be a significant difference.

RESULTS

Genotyping of UGT1A1*6/*28 in cancer patients with irinotecan treatment

A total of 106 cancer patients analyzed in this study included 66 males, 40 females, and the median age was 56 years (range 21 - 79 years). The genotyping results tested and analyzed by Automatic Hybridization (Baio, Shanghai) were shown in Figure 1. We further confirmed the genotyping results of these cancer patients with sequencing (Figure 2). The genotyping determined by PCR-chip hybridization was in accordance with the sequencing results.

When it comes to gene polymorphism, as shown in Table 1, the frequencies of GG, GA, and AA genotypes for UGT1A1*6 and TA6/TA6, TA6/TA7, and TA7/TA7 for UGT1A1*28 were 78.3% (n = 83), 19.8% (n = 21), 1.89% (n = 2) and 76.4% (n = 81), 17.9% (n = 19), 5.66% (n = 6), respectively. Four patients (3.77%) carried double heterozygosity (GA concurrent with TA6/TA7), other genotyping results occurred as shown in Table 1. We divided patients into three groups according to their genotypes: wild type (GG/TA6/6), heterozygous mutation (GA/TA6/7), and homozygous mutation (TA7/7), and no significant differences were seen between UGT1A1*6/*28 variants and patients' gender, age, primary tumor sites, and so on.

Table 3. Correlation of UGT1A1*6&*28 polymorphisms with diarrhea.

Genotyping	Patients with different grade of diarrhea (%)					p
	0	I	II	III	IV	
UGT1A1*28						p < 0.001
TA6/6 (n = 81)	78	1	1	1	0	
TA6/7 (n = 19)	9	2	2	4	2	
TA7/7 (n = 6)	0	1	1	4	0	
UGT1A1*6						p = 0.608
GG (n = 83)	69	2	3	8	1	
GA (n = 21)	16	2	1	1	1	
AA (n = 2)	2	0	0	0	0	

Table 4. Correlation of UGT1A1*6&28 polymorphisms with hematologic toxicity.

Genotyping	Hematologic toxicity (%)					p
	0	I	II	III	IV	
UGT1A1*28						p = 0.607
TA6/6 (n = 81)	24	24	23	8	2	
TA6/7 (n = 19)	5	4	7	1	2	
TA7/7 (n = 6)	1	2	1	2	0	
UGT1A1*6						p = 0.011
GG (n = 83)	26	27	24	5	1	
GA (n = 21)	4	3	7	4	3	
AA (n = 2)	0	0	0	2	0	

Table 5. Correlation of UGT1A1*6&*28 polymorphism with hematologic toxicity.

Hematologic toxicity	Grade	DW 62 (58.49)	SV 40 (37.74)	DV 4 (3.77)	p
Leukopenia	0 - 2	59 (95.16)	35 (87.5)	3 (75)	0.01
	3 - 4	3 (4.84)	5 (12.5)	1 (25)	
Neutropenia	0 - 2	59 (95.16)	32 (80)	2 (50)	0.004
	3 - 4	3 (4.84)	8 (20)	2 (50)	
Thrombocytopenia	0 - 2	61 (98.39)	37 (92.5)	3 (75)	0.055
	3 - 4	1 (1.61)	4 (7.5)	1 (25)	
Reduction of hemoglobin	0 - 2	61 (98.39)	38 (95)	4 (100)	0.206
	3 - 4	1 (1.61)	2 (5)	0	

Analysis of irinotecan-induced toxicity

In this study, severe delayed-onset diarrhea occurred in 11 patients (10.38%, 11/106), and 15 patients (14.15%, 15/106) developed severe neutropenia (Table 2). In our cohort, there were no associations between the toxicity (diarrhea and neutropenia) and patients' gender, age, chemotherapy regimens, primary tumor sites, and so on (all $p > 0.05$).

Table 6. Correlation of UGT1A1*6&28 polymorphisms with clinical response.

Genotyping	Clinical response			p
	PD	SD	PR	
UGT1A1*28				**p = 0.354**
TA6/6	**12**	**63**	**6**	
TA6/7	**3**	**16**	**0**	
TA7/7	**0**	**5**	**1**	
UGT1A1*6				**p = 0.299**
GG	**10**	**66**	**7**	
GA	**5**	**16**	**0**	
AA	**0**	**2**	**0**	

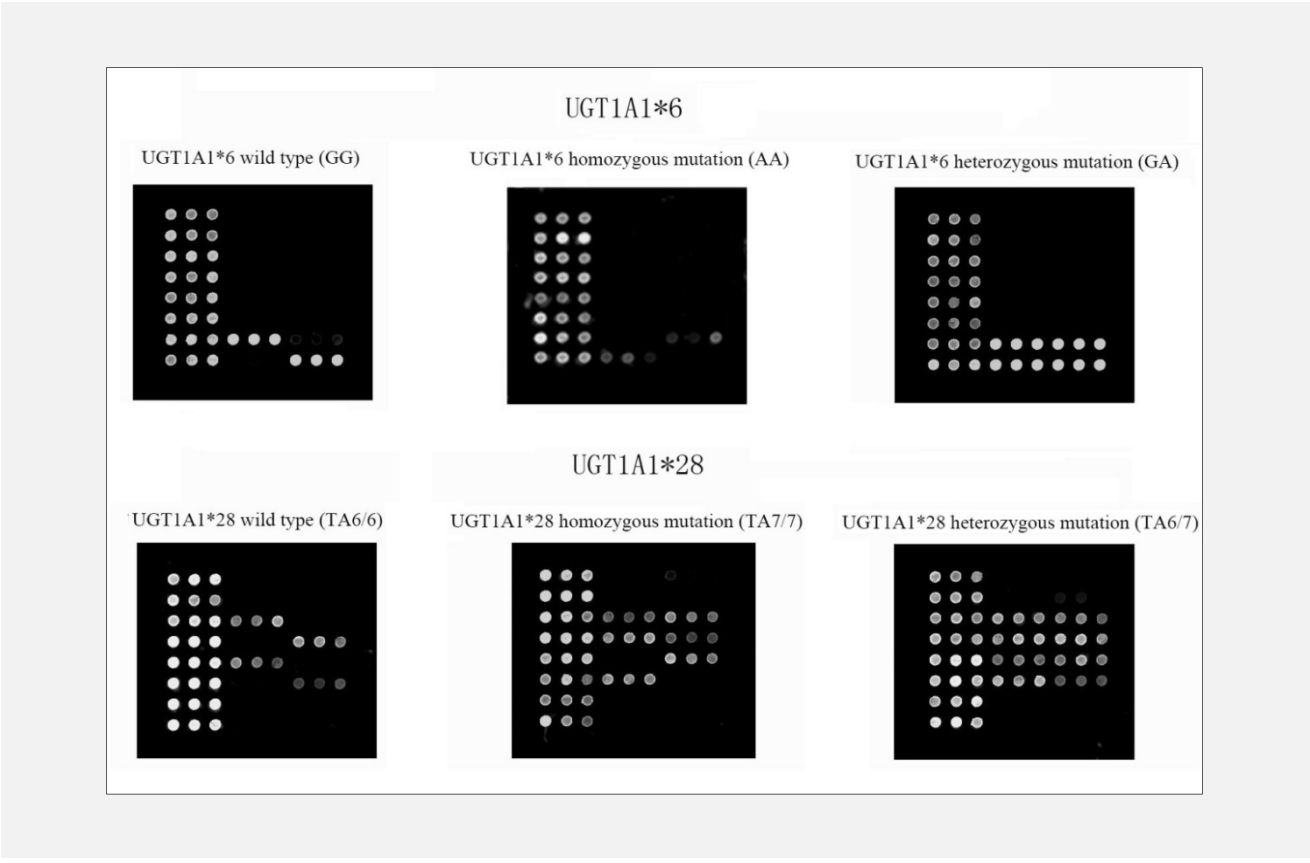

Figure 1. Genotype results determined and analyzed by Automatic Hybridization.

Correlation of UGT1A1*6/*28 polymorphisms with irinotecan toxicity

No significant differences of severe diarrhea were found in patients with GG (10.84%, 9/83), GA (9.5%, 2/21), and AA (0%, 0/2) genotypes (p = 0.608). However, the incidence of severe diarrhea in patients with TA7/7 genotype (66.7%, 4/6) was significantly higher than that in patients with TA6/7 (31.5%, 6/19) or TA6/6 (1.28%, 1/78) genotypes (p < 0.001) (Table 3). According to our results, UGT1A1*28 was more correlated with severe diarrhea than UGT1A1*6 genotype.

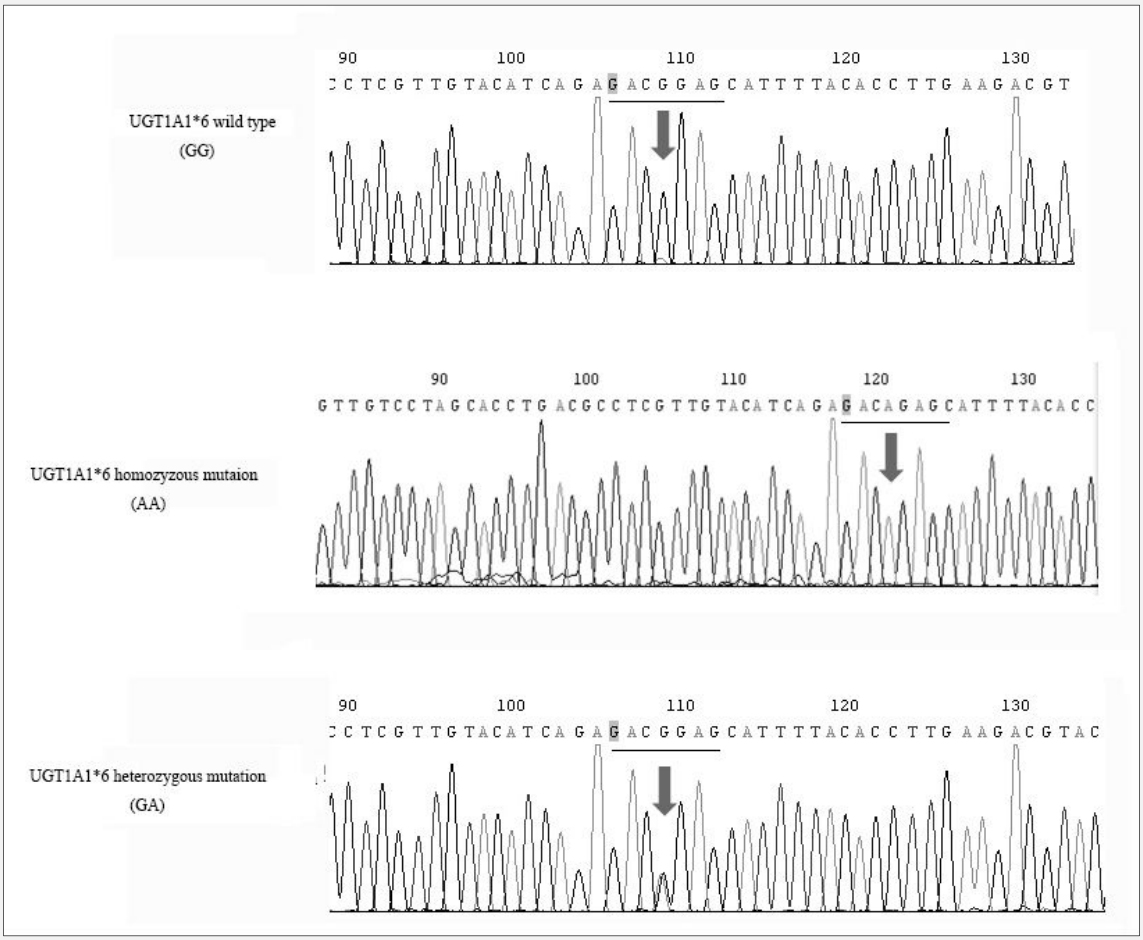

Figure 2. Sequencing of UGT1A1*6 genotype. The results were in accordance with PCR-chip hybridization.

When it comes to hematologic toxicity, things seem different. No significant differences of severe hematologic toxicity were found in patients with TA6/6 (12.34%, 10/81), TA6/7 (15.8%, 3/19), and TA7/7 (33.3%, 2/6) genotypes (p = 0.607). However, the incidence of severe hematologic toxicity in patients with AA (100%, 2/2) was significantly higher than that in patients with GA (33.3%, 7/21) or GG genotype (7.23%, 6/83) genotypes (p = 0.011) (Table 4). However, we noticed that only two patients carried AA genotype, so the results above need more data to be confirmed.

Additionally, a previous study reported that patients with double heterozygosity had a higher risk of developing severe toxicity. In order to precisely clarify UGT1A1 double heterozygosity genotype with hematologic toxicity, we first divided hematologic toxicity into four types: leukopenia, neutropenia, thrombocytopenia, and reduction of hemoglobin and analyzed each type with UGT1A1 mutations. According to our results, significant differences were found among double wild type (DW), single allele variant (SV), and double alleles variants (DV) in leukopenia and neutropenia (p = 0.01, p = 0.004) while no significant differences with platelets and hemoglobin were observed. These results suggest double allele variants may have higher risk for hematologic toxicity, especially for leukopenia and neutropenia (Table 5).

Correlation of UGT1A1*6/*28 polymorphisms and toxicities with clinical response

One hundred six patients receiving irinotecan containing chemotherapy were evaluated for clinical response. The number of patients with PR, SD, and PD were 15, 84, and 7, respectively. No significant differences were observed between UGT1A1*6 (p = 0.299) or UGT1A1 *28 (p = 0.355) polymorphisms and clinical response. Also, there were no obvious differences between severe toxicity and clinical response (Table 6).

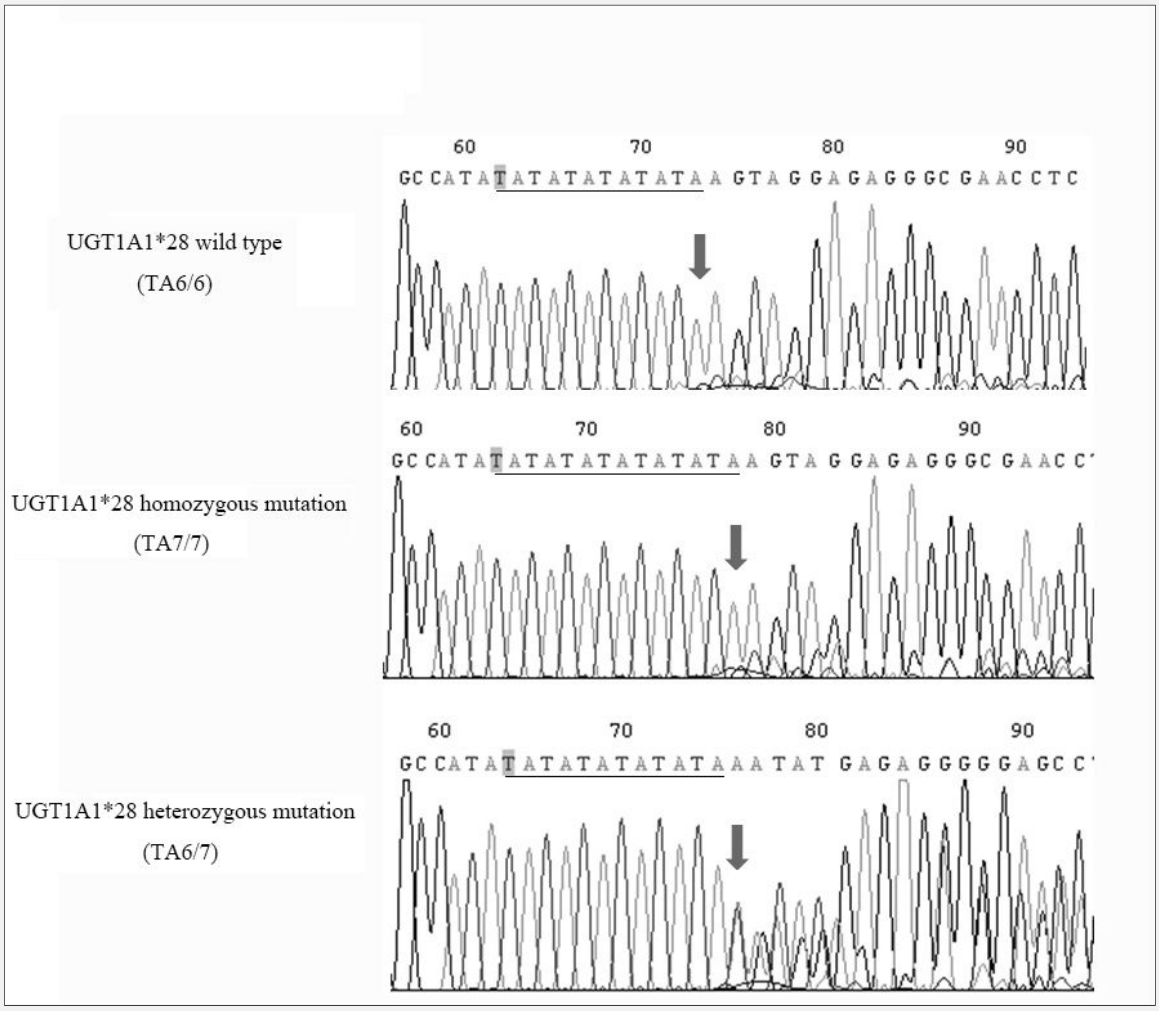

Figure 3. Sequencing of UGT1A1*28 genotype. The results were in accordance with PCR-chip hybridization.

DISCUSSION

Irinotecan, an anticancer drug that inhibits topoisomerase I, plays an important role in chemotherapy against colorectal cancer, lung cancer, gastric cancer, etc. However, IRI-induced toxicity such as neutropenia and diarrhea restricts its clinical application to a great extent. Nowadays clinical administration dosage is generally calculated according to the body surface area or weight which is the group average dose. However, only some of the drugs calculated as above may get satisfactory effects and tolerable toxicity. The small changes in plasma concentration that are affected by drug absorption, distribution, metabolism, and excretion may cause efficacy differences and lead to serious adverse effects. One of the main factors that affect the above process is UGT1A1 polymorphism. In order to avoid the side effect and get desired efficacy, it is of great necessity to develop anti-tumor therapy entering the era of individualized treatment through the use of biological markers, such as drug metabolism genes. The US Food and Drug Adminstration (FDA) has informed that individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia and amended the label of irinotecan in 2004. However, due to the variety and diversity of races, UGT1A1 polymorphism distribution is different in China and even varies from area to area. Therefore, there is a clear need for clinical participation to detect and collect the information regarding the correlation between UGT1A1 polymorphism and irinotecan toxicity so as to avoid severe side effects in clinical application.

Recent studies in some Asian countries indicate that the polymorphism of UGT1A1*6 has a similar effect as UGT1A1*28 on irinotecan-induced toxicity. However, it is unclear whether simultaneous heterozygous UGT1A1*28 and UGT1A1*6(TA6/7+G/A genotype) polymorphisms may have significantly more side effects and impacts on PK of SN38. Irinotecan PK is determined by multiple metabolizing enzymes, whereas the saturation of enzymatic reactions is affected by other factors, such as age and creatine clearance [7-9]. Presently, the dominant method for UGT1A1 gene detection is sequencing, nevertheless, it is only applied in research in China at the moment. The CYP2C19 gene chip that was developed by Shanghai Baio Ltd is the first diagnostic reagent approved by SFDA in China. Genotype technology that applied in this research work is based on a similar technology to CYP2C19. We detected the UGT1A1*6&*28 by gene chip and confirmed the results with sequencing one by one, so that we obtained all the UGT1A1*6&*28 polymorphisms of patients receiving irinotecan treatment in Jiangxi Province. According to our results, UGT1A1*6 plays a more vital role in hematologic toxicity ($p = 0.011$) whereas UGT1A1*28 is more involved in diarrhea $p < 0.001$). Additionally, simultaneous heterozygous UGT1A1*28 or UGT1A1*6 polymorphisms may produce higher exposure to SN-38 and a higher risk of adverse effects related to irinotecan. Due to adverse effects, the dose of irinotecan may be reduced or treatment delayed, which may affect the progression-free survival and overall survival of patients. Further studies should be done to explore the individualized treatment of irinotecan according to the genotype of UGT1A1*6/*28.

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Declaration of Interest:
The authors declare no conflict of interest.

References:

1. Han FF, Guo CL, Yu D, et al. Associations between UGT1A*6 or UGT1A1*6/*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients. Cancer Chemother Pharmacol 2014;73(4):779-88 (PMID: 23783485).

2. Iyer L, Das S, Janisch L, et al. UGT1A1*28 polymophism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2(1):43-7 (PMID: 11990381).

3. Iyer L, King CD, Whitington PF, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest 1998;101:847-54 (PMID: 9466980).

4. Minami H, Sai K, Saeki M, et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28. Pharmacogenet Genomics 2007;17:497-504 (PMID: 17558305).

5. Sunakawa Y, Ichikawa W, Fujita K, et al. UGT1A1*1/*28 and *1/*6 genotypes have no effects on the efficacy and toxicity of FOLFIRI in Japanese patients with advanced colorectal cancer. Cancer Chemother Pharmacol 2011;68:279-84 (PMID: 20957 480).

6. Shulman K, Cohen I, Barnett-Griness O, et al. Clinical implications of UGT1A1*28 genotypes testing in colorectal cancer patients. Cancer 2011;117:3156-62 (PMID: 21287524).

7. Miya T, Goya T, Fujii H, et al. Factors affecting the pharmacokinetics of CPT-11: the body mass index, age and sex are independent predictors of pharmacokinetic parameters of CPT-11. Invest New Drugs 2001;19:61-7 (PMID: 11291833).

8. Isaakidou A, Gazouli M, Aravantinos G, Pectasides D, Theodoropoulos GE. Prediction of response to combination chemotherapy with irinotecan in Greek patients with metastatic colorectal cancer. J Cancer Res Ther 2016;12(1):193-7 (PMID: 27072236).

9. Wang W, Huang J, Tao Y, et al. Phase II and UGT1A1 polymorphism study of two different irinotecan dosages combined with cisplatin as first-line therapy for advanced gastric cancer. Chemotherapy. 2016;61(4):197-203 (PMID: 26872008).

Supplementary Table

No.	Cancer type	Age	Gender type	Weight	Tumor situation	Liver function	Renal function
1	Colon cancer	41	M	85	metastasis to lung and liver	normal	normal
2	Colon cancer	51	F	45	metastasis to nodules of sigmoid colon wall, pelvic floor, abdominal wall	normal	normal
3	Colorectal cancer	58	M	56	metastasis to liver	normal	normal
4	Lung cancer	26	M	59	metastasis to brain and bone	normal	normal
5	Colon cancer	29	M	67	lymphatic metastasis	normal	normal
6	Colon cancer	69	M	73	lymphatic metastasis	normal	normal
7	Colorectal cancer	79	M	68		normal	normal
8	Colon cancer	64	F	79	lymphatic metastasis	normal	normal
9	Colon cancer	27	F	67	no metastasis	normal	normal
10	Gastric cancer	60	F	40	lymphatic metastasis	normal	normal
11	Colorectal cancer	51	F	49	lymphatic metastasis	normal	normal
12	Colon cancer	48	F	46	liver metastasis	normal	normal
13	Colorectal cancer	60	M	55	no metastasis	normal	normal
14	Carcinoma of urinary bladder	38	M	57	metastasis to lung and liver	normal	normal
15	Colon cancer	62	F	54	infringement of nerve tissue, cancer cells infiltrating in the surrounding mesentery	normal	normal
16	Colon cancer	63	F	69	liver metastasis	normal	normal
17	Colorectal cancer	74	F	55	lymph node metastasis; lung, liver metastasis	normal	normal
18	Colorectal cancer	52	F	68	pulmonary metastasis	normal	normal
19	Cancer of duodenum	50	F	57	no metastases	normal	normal
20	Colorectal cancer	68	F	75	lymph node metastasis; pulmonary metastasis	normal	normal
21	Colon cancer	53	M	44	metastatic lung cancer; cerebral metastatic carcinoma	normal	normal
22	Colorectal cancer	59	M	65	no metastases	normal	normal
23	Colorectal cancer	46	F	51	secondary malignant liver tumors	normal	normal
24	Carcinoma of the lung	68	F	58	no metastases	normal	normal
25	Lung cancer	48	M	49	no metastases	normal	normal
26	Carcinoma of the lung	40	M	51	the thoracic vertebrae metastasis	normal	normal
27	Colorectal cancer	72	F	60	abuse and full-thickness	normal	normal
28	Cancer of the stomach	58	F	49	lymphatic metastasis	normal	normal
29	Colorectal cancer	68	F	59	lymphatic metastasis	normal	normal
30	The left lung malignancy	52	F	55	no metastases	normal	normal
31	Colon cancer	69	F	55	liver metastases	normal	normal
32	Colon cancer	68	F	69	lung, bone metastases	normal	normal
33	Colorectal cancer	57	F	85	lymphatic metastasis; bone soft tissue metastasis	normal	normal
34	Colorectal cancer	43	F	65	pelvic metastasis; lymphatic metastasis	normal	normal
35	Colon cancer	55	M	42,5	liver metastases	normal	normal
36	Colorectal cancer	47	F	57	lung metastases	normal	normal

No.	Cancer type	Age	Gender type	Weight	Tumor situation	Liver function	Renal function
37	Colorectal cancer	41	F		lymphatic metastasis; liver metastases	normal	normal
38	Colon cancer	68	M	42	lymphatic metastasis	normal	normal
39	Colorectal cancer	47	M	58	bone metastases; pulmonary metastases	normal	normal
40	Carcinoma of the lung	71	F	59	liver metastases; secondary bone malignant tumors	normal	normal
41	Carcinoma of the lung	42	F	60	secondary malignant brain tumor	normal	normal
42	Colon cancer	72	F	48	secondary malignant liver tumors	normal	normal
43	Cardia cancer	59	F	65	no metastasis	normal	normal
44	Pulmonary malignant tumor	60	F	65	lymphatic metastasis	normal	normal
45	Cancer of the stomach	42	M	50	lymphatic metastasis	normal	normal
46	Cancer of the stomach	53	F	43	secondary malignant ovarian tumors	normal	normal
47	Cancer of the stomach	59	F	72	secondary malignant liver tumors; lung secondary malignant tumor; secondary malignant bone tumors	normal	normal
48	Colorectal cancer	57	M	77,5	secondary malignant liver tumors; lung secondary malignant tumor	normal	normal
49	Colorectal cancer	70	F	59	secondary malignant liver tumors	normal	normal
50	Colon cancer	72	M	47	lung secondary malignant tumor	normal	normal
51	Colon cancer	60	F	69	secondary malignant liver tumors	normal	normal
52	Colorectal cancer	59	F	58	no metastasis	normal	normal
53	Right pulmonary malignant tumor	52	F	49	pulmonary metastasis	normal	normal
54	Colorectal cancer	32	F	58	lymphatic metastasis	normal	normal
55	Colorectal cancer	58	F	73	no metastasis	normal	normal
56	Colon cancer	50	M	39	lymphatic metastasis	normal	normal
57	Pulmonary malignant tumor	67	M	The wheelchair	lymphatic metastasis	normal	normal
58	Colon cancer	60	M	46	no metastasis	normal	normal
59	Colorectal cancer	70	M	67	lymphatic metastasis	normal	normal
60	Small cell lung cancer	70	M	59	lymphatic metastasis; metastasis to liver	normal	normal
61	Colorectal cancer	49	F	69	no metastasis	normal	normal
62	Small cell lung cancer	62,5	M	66	lymphatic metastasis	normal	normal
63	Colon cancer	46,5	F	60	Liver metastasis; lung metastasis	normal	normal
64	Colon cancer	73	F	63	no metastasis	normal	normal
65	Colorectal cancer	70	M	35	lung metastases	normal	normal
66	Colorectal cancer	80	F	59	liver metastasis; lymphatic metastasis	normal	normal
67	Colorectal cancer	75	M	56	liver metastasis; lymphatic metastasis	normal	normal
68	Gastric cancer	59	F	46	no metastasis	normal	normal

No.	Cancer type	Age	Gender type	Weight	Tumor situation	Liver function	Renal function
69	Colorectal cancer	45	F	71	liver metastasis	normal	normal
70	Colon cancer	58	M	63	lymphatic metastasis	normal	normal
71	Colorectal cancer	54	F	71	breast metastasis	normal	normal
72	Colorectal cancer	56	M	33	liver metastasis	normal	normal
73	Gastric cancer	48,5	F	57	lymphatic metastasis	normal	normal
74	Colorectal cancer	50	F	51	Lu	normal	normal
75	Colon cancer	54	F	71	liver and lung metastasis	normal	normal
76	Colorectal cancer	50	M	51	no metastasis	normal	normal
77	Colon cancer	41,5	F	45	no metastasis	normal	normal
78	Colon cancer	55	M	62	no metastasis	normal	normal
79	Colorectal cancer	58	F	39	lung metastases	normal	normal
80	Small cell lung cancer	83	M	59	no metastasis	normal	normal
81	Colorectal cancer	65	M	53	lymphatic metastasis	normal	normal
82	Small cell lung cancer	72	M	67	lymphatic and liver metastasis	normal	normal
83	Small cell lung cancer	57	M	66	lymphatic metastasis	normal	normal
84	Lung cancer	72	M	69	lymphatic metastasis	normal	normal
85	Lung cancer	84	M	61	liver and bone metastasis	normal	normal
86	Colorectal cancer	56	M	26	liver metastasis	normal	normal
87	Gastric cancer	40	F	40	liver metastasis and lymphatic metastasis	normal	normal
88	Colorectal cancer	55	M	46	liver metastasis	normal	normal
89	Colorectal cancer	58,5	M	61	no metastasis	normal	normal
90	Colorectal cancer	40	F	35	metastasis to oophoron	normal	normal
91	Non-small cell lung cancer	45	F	56	no metastasis	normal	normal
92	Small cell lung cancer	60	M	62	no metastasis	normal	normal
93	Colorectal cancer	59	M	70	no metastasis	normal	normal
94	Colon cancer	66	M	51	lymphatic and lung metastasis	normal	normal
95	Small cell lung cancer	69	M	59	liver and bone metastasis	normal	normal
96	Colorectal cancer	58	M	47	no metastasis	normal	normal
97	Gastric cancer	48	M	63	lymphatic metastasis	normal	normal
98	Small cell lung cancer	60	M	57	metastasis to brain	normal	normal
99	Gastric cancer	42	F	75	metastasis to lung	normal	normal
100	Colorectal cancer	50	F	77	no metastasis	normal	normal
101	Colorectal cancer	43	F	74	lung metastasis	normal	normal
102	Colorectal cancer	61	M	60	liver metastasis	normal	normal
103	Colon cancer	75	M	63	no metastasis	normal	normal
104	Colorectal cancer	64	M	41	no metastasis	normal	normal
105	Colon cancer	72	M	68	no metastasis	normal	normal
106	Colorectal cancer	57	F	60	lung and bone metastasis	normal	normal