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Comprehensive Look toward Irinotecan Toxicity based on Genetic Differences, Concerning UGT1A1

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Abstract

The two most limiting toxicities in regard with Irinotecan therapy are leukopenia and diarrhea. Today, we know that SN-38, as an active drug metabolite, is responsible for both antitumor activities and adverse effects. After implementing of the desired therapeutic effects, glucuronidation of SN-38 by UDP-Glucuronosyltransferase (UGT) 1A enzymes leads to generation of inactive form. In worldwide ethnicities, there is a difference in frequency of genotypes the UGT1A1 and rate of toxicity occurrence. We have reviewed the UGT 1A1 polymorphisms and reported associated toxicities in different studies by different ethnicities and chemotherapy regimens including Irinotecan. We reconfirmed the probable association of irinotecan related adverse effects according to polymorphism differences of the UGT 1A1 enzyme. In different settings, the frequency of the adverse effects varies substantially. Thus, patients' treatment strategy must be adjusted according to genetic variations and prevalence of toxicity on geographical area.

Keywords: Irinotecan; UDP-glucuronosyltransferase; Polymorphisms; Colorectal cancer; Adverse effects

Introduction

Irinotecan, is a famous key agent in first-line chemotherapy regimen for treatment of Metastatic Colorectal Cancer (MCRC) [1], the initial form is prodrug that will be metabolized by carboxylesterase to 7-ethyl-10-hydroxycamptothecin (called SN-38). The metabolite, SN-38, exerts antitumor activities as well as toxicities. Subsequently, SN-38 converts to inactive form *via* glucuronidation, after therapeutic effects implemention [2]. The conversion mainly performs by UDP-Glucuronosyltransferase (UGT) 1A enzyme, while UGT1A1 isoform has a major role in the inactivation of SN-38 [3].

Irinotecan is commonly prescribed for advanced MCRC chemotherapy regimen as a single agent [4] or in combination with a fluoropyrimidine [5-7] with or without a monoclonal antibody [8]. Despite of wide use of irinotecan, especially for colorectal cancer [9], there are great concerns about dose-limiting toxicities associated by drug administration such as leukopenia and diarrhea [10]. The worry is to some extent that the ministry of health in Japan has been banned irinotecan administration in unequipped medical institution without experienced specialists in chemotherapy [11].

Previous study reported up to 35% probability of fatal toxicities with irinotecan's use as a single-agent in chemotherapy regimen [12] and they noted a rising rate of early deaths in patients receiving chemotherapy regimens containing irinotecan and fluorouracil [12]. It was estimated that irinotecan's main adverse effects, diarrhea and neutropenia, have the prevalence of 20% and 35%, respectively [13-16]. Depending on The administrative doses and type of chemotherapy regimens, the incidence of grade 3 or 4 hematological toxicity varies between 5% up to 33% [17]. Hospitalization due to irinotecan administration has been mostly reported as a result of diarrhea (18%) and leukopenia/neutropenia (8%) [18]. There are two forms of irinotecan related diarrhea; acute form and late form. Due to cholinergic nature of acute form of diarrhea, subcutaneous administration of atropine can prevent it in almost all of the suffering patients. On the other hand, the mechanisms of late diarrhea, occurs beyond 24 hours after irinotecan administration, is unknown and may become prolonged and life-threatening due to dehydration and electrolytes' imbalance [19]. Destruction of gastro-intestinal mucosa results in translocation of gut flora and induces systematic infections especially in patients with concomitant symptoms of diarrhea and neutropenia. Febrile neutropenia is mostly associated with grade 3 or 4 diarrhea [20]. Late onset diarrhea can be treated best with high-dose of oral loperamide as soon as the patient reports loose stools [15].

Recently, individualization of drug therapy for each patient is a new challenge in pharmacotherapy era. Drug individualizing therapy is even most important in medical oncology comparing to other areas of medicine [13]. In some cancer patients treated with chemotherapy, both activation of a pro-drug and metabolism of active compounds might be affected by lower enzymatic activity leads to either diminished therapeutic effect or severe toxicity [14].

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Table 1: The frequency of reported genotypes in different countries.

Factor Country [references]	Population Size	Dose / regimen	Allele frequency (%)				UGT1A1*28 Genotype frequency (%).			UGT1A1*6 Genotype frequency (%).			UGT1A1*60 Genotype frequency (%).			UGT1A1*27 Genotype frequency (%).		
			*28	*6	*60	*37	*28*1	*28*28	*1*1	*6*1	*6*6	*1*1	*60*1	*60*60	*1*1	*27*1	*27*27	*1*1
Thailand. [35]	44	-	12.5	8			20.5	2.3	77.3	15.9	0	84.1						
Japan. [36]	795	-					16.6	1.5		24.6	1.8							
Japan. [37]	27	30mg/m^2 Day 1-3 q 28 days					11.1			18.5								
Japan. [38]	1312	125-150 mg/m^2					17.6	1.8		23.5	3.8							
Japan. [39]	21	80-150 mg/m^2 q2 weeks day1					19			23								
Japan. [40]	75	150mg/m^2								30.7	2.7	66.7	38.7	8	53.3	2.7	0	97.3
Japan. [41]	28	70-150mg/m^2 q 2 weeks					21.4	0	78.5									
Japan. [42]	10	q 2 weeks FOLFOXIRRI																
Japan. [43]	30	q 4 weeks Day1,8,15 60mg/m^2					13	0		27	0					0	0	0
Japan. [44]	75	60mg/m^2 q1-2 weeks 100-160mg/m^2 q2 week																
Japan. [45]	118	<60, 60, >60mg/m^2 total actual dose <300, 301-600, >600 q 1-4 weeks, twice q 4 weeks					19.7			10.6								
North Korea. [46]	50	200-350 mg/m^2 day1 q 3 weeks					12	4		28	6							
North Korea. [47]	30	-	10.3	15.5														
North Korea. [48]	43	250-500mg/m^2								14	9.3		21	6.97				
Republic of China. [49]	41	80-125 mg/m^2 day1 q 2 weeks					8	0	80	46.2	2.6	51.3						
Republic of China. [50]	276	180mg/m^2					19.9	1.1	79	28.6	6.9	64.5						
Three Asian countries. [33]	269	375 mg/m^2 q 3 weeks					33	6.4	60	13	1.11	85.7						
	45						33.3	0	66.6	17.7	4.4	77.7						
United Sates. [51]	68	400-1000 mg/m^2 q 3 weeks					41.1	13.2	45.5									
Spain. [52]	95	350mg/m^2 q 3 weeks 80mg/m^2 q 2 weeks 180mg/m^2 q 2 weeks	34				47.3	10.5	42									
Saudi Arabia. [53]	192	-	25.7	0	62.4	0.5	47.9	1.4	50				54	35.4	10.6	0	0	0
Iran. [54]	300	-		6.83						13	0.33							

The available data were reported

As mentioned above, hydrolysis of the irinotecan by carboxylesterases generates SN-38, an active topoisomerase I inhibitor, [16]. Uridine diphosphate glucuronosyltransferase 1As (UGT1As), such as 1A1, 1A7, 1A9 and 1A10, subsequently, glucuronidates SN-38 to generate the inactive form (SN-38G) (27-30). UGT1A1, among the UGT isoenzyme, is thought to have the most contribution in SN-38G formation as well as termination of its therapeutic impacts and its adverse effects [3,21].

Changes in the number of TA (Thymidine-Adenine) nucleotides that repeats in the TATA box of UGT1A1 promotor, result in the UGT1A1*28 polymorphism emerged from the wild-type with six repeats to the seven repeats variant. UGT1A1*28 emersion leads to diminishing enzyme activity and reduction in SN-38 glucuronidation in human [19,22-24]; beside, it is considered a risk factor for the occurrence of toxicity. Based on evidences with adequate strength, irinotecan-related neutropenia is more prevalent in patients with UGT1A1*28/*28 genotype [17,25-27]. However, the exact relationship between UGT1A1*28 variant and severe diarrhea needs to be confirmed in further assessment. However, there are several studies reported associations between the UGT1A1*28 genotype and diarrhea, [26,28,29] while the association was not statistically significant in other similar studies [30-34].

Between different ethnicities in the world, there is variation in frequency of UGT1A1 polymorphisms and subsequently incidences of toxicities. Results from different studies were not uniform in reporting the frequencies of different UGT1A1genotypes and possible association by potential serious adverse effects. In this review, we gathered all data around UGT1A1 polymorphisms and related frequency of toxicity which were reported in different studies. We included all data in cancer patients with different ethnicities, emphasizing on Asian population, receiving different dose and irinotecan containing chemotherapy regimens.

Methods

We conducted a literature search based on frequency of UGT 1A1 enzyme polymorphisms and irinotecan toxicities. All data obtained by searching ELSEVIER, PubMed, web of knowledge, clinical trials, Scopus, and Cochrane database of systematic reviews, related

clinical studies. The patients with different ethnicities and diverse chemotherapy regimens containing irinotecan were implemented. We also prospectively collected data in all admitted cancer patients in our hospital, Omid hospital, Isfahan, Iran, who received irinotecan containing regimen in order to check the prevalence of irinotecan related diarrhea and neutropenia in last year in our local center.

Results

Thai population

In Thai population affected by colorectal cancer as reported in a retrospective study, the frequencies of genetic testing of TA6/TA6, TA6/TA7, TA7/ TA7 for UGT1A1*28 were 77.3% (34/44), 20.5% (9/44) and 2.3% (1/44), while the reported frequencies of GG, GA for UGT1A1*6 were 84.1% (37/44) and 15.9% (7/44), respectively. No patients were homozygous for UGT1A1*6 (AA). Results of a pooled analysis of UGT1A1*28 and *6 frequencies revealed three divided groups: wild type (TA6/TA6 and GG, 63.7%, 28/44), heterozygous mutations (TA6/TA6 and GA; TA6/TA7 and GG; 31.8%, 14/44), and homozygous mutations (TA6/TA7 and GA; TA7/TA7 and GG; 4.5%, 2/44). The frequency of UGT1A1*28 and *6 allele was 0.125 and 0.080, respectively. Out of 44 patients, three subjects (6.8%) experienced sever neutropenia. The correlation between UGT1A1 *28 and *6 polymorphism (homozygous mutations; *28/*28, *28/*6) with irinotecan induced sever neutropenia, during first and second cycle of chemotherapy were analyzes and revealed significant association (P=0.04) [35] (See Table 1 and 2).

Japanese population

In reviewing of Japanese studies, following data were revealed: from 795 patients evaluated for UGT1A1 genotype, 50% of them were wild-type group while 41.1% were either *28 or *6 heterozygotes. In homozygous group (8.8%), 1.8% were homozygotes for *6 allele and 1.5% for *28. *28/*6 heterozygotes were 5.5% of all patients. After administration of FOLFIRI regimen which has been consisted of 150mg/m^2 irinotecan in colorectal cancer patients, all adverse effects of grade 3-4, occurred in 63% of patients (500/795) and grade 3-4 neutropenia observed in 50% of patients (395/795). The incidence of grade ≥3 neutropenia throughout the treatment tended to be increased in the following order, wild-type < heterozygous < homozygous (44.7, 54.1, and 57.1%, respectively). 1.67-fold and 2.22-fold increase in overall risk (OR) of grade ≥3 neutropenia respectively was revealed for heterozygous and homozygous groups in comparison to wild-type group [36].

Of the 27 patients with relapsed or refractory Diffuse Large B-Cell Lymphoma (DLBL) who were older than 60 years tested for the UGT1A1*6 and *28 genotypes, five patients (18.5%) were heterozygous for UGT1A1*6 and three (11.1%) for *28. Seven patients had UGT1A1*6 polymorphism. Following adverse effects observed with a regimen included irinotecan 30mg/m^2/day, day 1-3 every 28 days: Leukopenia grade 4 in 74% (20/27), neutropenia grade 4 in 89% (24/27), febrile neutropenia in 82% (22/27), grade 1-2 diarrhea in 19% (5/27), thrombocytopenia grade 3-4 in 41% (11/27), anemia grade 3 in 56% (15/27), nausea and vomiting in 11% (3/27) and abdominal pain grade 1 in 7% (2/27). UGT1A1*6 was associated with hematological adverse effects (sever neutropenia in 100% with UGT1A1*6 polymorphism), but not with gastrointestinal toxicities [37].

In 1312 patients with advanced colorectal cancer, The UGT1A1 genotype was wild-type in 47.9% of the patients, heterozygous in 41.1%, and homozygous in 11.1%. In 1312 patients who received irinotecan doses of 125-150mg/m^2 as FOLFRI or with S1 or monotherapy, grade 3-4 neutropenia observed in 413 patients (31.5%) and grade 3/4 diarrhea in 54 patients (4.1%). Severe neutropenia of grade 3 or 4 was more common in the homozygous group (P=0.0001 in the entire cycle) and heterozygous group (P=0.0010 in the entire cycle) than in the wild-type group [38].

Frequencies of UGT1A1*6 and *28 gene polymorphisms in a 21 patient population study were found to be 19% and 23%, respectively. 11 patients (52.4%) were wild type, 4 (19%), 5 (23%) and one patient (4.8%) were heterozygotes for *28, *6 and *28/*6, respectively. Most common adverse effects were leucopenia, neutropenia, diarrhea, anorexia, and nausea (19-20/21 of patients, 90-95%). Grade 3 or 4 adverse effects observed as follows: neutropenia in 13/21 (62%), leukopenia in 5/21 (24%), vascular events in 2/21 (10%), and severe diarrhea in 1/21 (5%). No significant differences revealed from analyses of the relationships between adverse effects and UGT1A1 polymorphism despite previous reports [39].

Additionally, among 75 studied patients, 50/75 (66.7%), 23/75(30.7%) and 2/75 (2.7%) were wild, heterozygous and homozygous for UGT1A1*6; respectively. 73/75 (97.3%) were wild-type and 2/75 (2.7%) were heterozygous for UGT1A1*27. For UGT1A1*28 and *93; 59/75 (78.7%) had wild-type genotype, 14/75 (18.7%) were heterozygote and 2/75(2.7%) were homozygote. 40/75 (53.3%), 29/75 (38.7%) and 6/75 (8%) were wild, heterozygote and homozygotes for UGT1A1*60, respectively. Grade 3-4 hematologic toxicities were noted in 45% (34/75) of metastatic colorectal cancer patients who received irinotecan 150mg/m^2 every two weeks in a FOLFRI regimen whether as first or second line. Severe hematological toxicity was observed in all *28/*6 and *6/*6 patients. During the entire course of therapy severe hematological adverse effects were more frequently reported in patients with UGT1A7*3 (387G) and UGT1A1*6 (211A) genotypes. For the latter finding, multivariate analysis revealed that UGT1A1*6 was the only significant predictor (P=0.022, odds ratio 3.00, 95% confidence interval (CI) 1.17-7.69). A grade 3 diarrhea was developed in only two patients (2.7%) who had UGT1A diplotype. Evaluation of UGT1A1*28,*6 and also UGT1A7*3 and UGT1A9*22 is very important to predict the toxicity of irinotecan in Japanese (or Asian) population. Although each UGT1A1*6 (211A), UGT1A7*3 (387G), and UGT1A9*22 (T9) allele can predict hematological toxicity, haplotype II (containing four risk alleles, UGT1A1*6, UGT1A7*3 [387G and 622C], UGT1A9*1 [T9]) and homozygosis of UGT1A1*28 and *6 were better predictors of such toxicity [40].

In another study, among 28 colorectal cancer patients, 22(78.5%) had the UGT1A1*1 (wild-type) allele (TA6⁄TA6) and six (21.4%) had the UGT1A1*28 (mutant) allele (TA6⁄TA7). 150mg/m^2 of irinotecan (70mg/m^2 in mutant UGT1A1*28) was administered every two weeks. Twenty three patients completed at least six cycles. Neutropenia and leukopenia occurred in 50% and 54%, respectively. Sever neutropenia was observed in 3/28 patients (10.7%), leukopenia in 2/28 (7.1%), diarrhea in 3/28 (10.7%), anorexia in 2/28 (7.1%), fatigue and nausea in 1/28 (3.6%). Toxicities in those with the *1*28 genotype who received 70mg/m^2 of irinotecan tended to be of lower

Table 2: The frequency of reported toxicities and polymorphism in different countries.

Factor Ethinicity [references]	Pooled frequency UGT1A1 *28 and *6 (%)			Pooled frequency UGT1A1 *28 and *93(%)			Frequency of *28*6 concurrently (%)	Frequency of *6*60 concurrently (%)	Frequency of *28*60 concurrently (%)	Frequency of severe neutropenia (%)	Frequency of severer diarrhea (%)	Severe adverse effects and polymorphism association (%)
	Heterozygous	Homozygous	Wild type	Heterozygous	Homozygous	Wild type						
Thai. [35]	31.8	4.5	63.7	-	-	-	-	-	-	6.8	-	*28 and *6 and G[1]3-4 neutropenia, both significant
Japanese. [36]	41.1	8.8	50	-	-	-	5.5	-	-	50	-	With G3-4 neutropenia OR[2]= 1.67 for wild *vs*. heterozygous. OR= 2.22 for wild *vs*. homozygous
Japanese. [37]	29.6	-	-	-	-	-	-	-	-	89	-	100% of patients harboring *6 experienced G3-4 neutropenia
Japanese. [38]	41.1	11.1	47.9	-	-	-	5.5	-	-	31.5	4.1	G3 neutropenea incidence in heterozygous vs, wild: P= 0.001 Homozygous *vs*. wild: P=0.0001
Japanese. [39]	42	0	52.4	-	-	-	4.8	-	-	62	5	Not significant
Japanese. [40]	-	-	-	18.7	2.7	78.7	-	-	-	45	2.7	*6 and G3-4 hematological P=0.02
Japanese. [41]	-	-	-	-	-	-	-	-	-	10.7	10.7	Lower toxicity in patients with mutant allel
Japanese. [42]	-	-	-	-	-	-	-	-	--	50	-	-
Japanese. [43]	40	0	57	-	-	-	3	-	-	40	16.6	P= 0.04 neutropenia in non-wild type. For *6: P= 0.014
Japanese. [44]	-	-	-	-	-	-	-	-	-	34,7	5.3	P=0.012 increase in with *6 allele
Japanese. [45]	30.3	-	-	-	-	-	-	-	-	40	18.5	P= 0.001 with *28 allele
Korean. [46]	40	10	46	-	-	-	4	-	-	26.1	17.4	Increase in G3-4 neutropenia in 1 defective allele group
Korean. [47]	31	0	58.6	-	-	-	10.3	-	-	53.4	16.7	P=0.043 neutropenia increase with increase in defective allele
Korean. [48]	-	-	-	-	-	-	-	-	-	53.5	9.3	P=0.018 lower neutropenia in no defective allele
Chinese. [49]	54.2	2.6	43.2	-	-	-	-	-	-	68.3	4.9	Not significant
Chinese. [50]	39.1	8	48.2	-	-	-	4.7	-	-	20.3	5.8	*6 with neutropenia: P=0.001 *28 with neutropenia P=0.029
Three Asian ethnicity. [33]	46 51.4	7.5 4.4	-	-	-	-	-	-	-	-	-	85% lower mean ANC in homozygous *6
American. [51]	-	-	-	-	-	-	-	-	-	75% of Dose limiting toxicities	25% of Dose limiting toxicities	-
Spanish. [52]	-	-	-	-		-	-	-	-	21	30.5	Between severe diarrhea and *28 allele P= 0.005
Saudi. [53]	-	-	-	-	-	-	-	-	16.2	-	-	-
Iranian. [54]	-	-	-	-	-	-	-	-	-	-	-	-

1: G: Grade

2: OR: Odds ratio

grade than in those with the *1*1 genotype who received 150mg/m^2 of irinotecan [41].

In a phase I study by Sunakawa et al, FOLFOXIRI was administered to 10 advanced colorectal cancer patients with UGT1A1 *1/*1 and *1/*28 or *1/*6, every two weeks. A median of 8.5 cycles of chemotherapy per patient was administered. Grade 3 and 4 toxicities were not common; except for neutropenia. They noted that 27% of chemotherapy cycles were associated with severs neutropenia while febrile neutropenia was not observed. Fifty percent of patients (5/10) had at least one episode of grade 3-4 neutropenia. They believed that excluding the patients with UGT1A1 *28/*28, *6/*6 or *6/*28 might have affected on patients better tolerance of treatment [42].

UGT1A1 genotyping of 30 patients with gynecologic cancers (ovarian and cervical), revealed that there was wild-type genome in 17 patients (57%), UGT1A1 *28 in 4 (13%), UGT1A1 *6 in eight (27%) and UGT1A1 *28 *6 in one (3%) patient; while, UGT1A1 *27 mutation was not observed in any of the 30 study patients. No homozygous polymorphisms were observed in this study. In these patients, who were administered irinotecan 60mg/m^2 in day 1, 8 and 15 with cisplatin every four weeks; following grade 3-4 adverse effects were occurred: leukopenia and diarrhea in 16.6% (5/30), neutropenia in 40% (12/30), thrombocytopenia in 10% (3/30), nausea in 23.3% (7/30) and vomiting in 36.6% (11/30). There was a significant increase in grade 3/4 toxicities in the UGT1A1 non-wild-type group. Neutropenia (p=0.04), thrombocytopenia (p=0.04) and diarrhea (p=0.005) were more frequently detected in the UGT1A1 non-wild-type group. Difference was more significant for UGT1A1*6 and p-values are as follows for mentioned toxicities: 0.014, 0.03, and 0.001. In final analyses, The UGT1A1 *6 genotype was an independent risk factor for grade 3/4 neutropenia (hazard ratio, 6.54; 95% confidence interval, 1.44-29.60) and grade 3/4 diarrhea (hazard ratio, 7.45; 95% confidence interval, 1.44-29.78) [43].

In 49 patients evaluated for polymorphism, 20 patients were wild type genotype, nine patients with *28/- genotype, 16 with *6/- genotype, two subjects with *6/*28 genotype and two were *6 homozygotes. No *28 homozygotes were enrolled. Irinotecan was administered as a single agent or in combination with other chemotherapy agents at 60mg/m^2 every one or two weeks, 100 and 160mg/m^2 every two weeks. Severe neutropenia was found in 26 of 75 subjects (34.7%); six patients in monotherapy regimen (49 subjects), 11 of 15 patients in combination with cisplatin, eight of nine patients in combination with mitomycin regimen and 1 of 2 patients in combination with 5-Fluorouracil group. Severe diarrhea noted in four of 75 (5.3%) of patients, one of 49 patients in monotherapy regimen and two of 15 patients in combination with CDDP and one of nine patients in combination with MMC regimen. The incidence of grade 3-4 neutropenia increased in dependent manner by *6 alleles (p=0.012 in chi square test analyses). Incidences of severe neutropenia were 2.3 fold and 15-fold higher in *6 heterozygotes (*6/*1, *6/*60 and *6/*28) and homozygotes (*6/*6), respectively, in comparison with incidences were seen in the non-*6 bearing patients (*1/*1, *60/*1, *28/*1, and *28/*60) [44].

In a study in which, 118 patients were enrolled allele frequency of UGT1A1*28 were 0.197 and 0.106 for UGT1A1*6. 26 of 118 (22.3%) cancer patients (lung, colorectal and others) experienced sever toxicity. Irinotecan doses was used less than 60, 60 and more than 60mg/m^2 for each infusion administered in 9 (35%), 8(31%) and 9(35%) of these patients, respectively. Total actual dose of irinotecan was less than 300mg/m^2 in 15(58%), 301-600mg/m^2 in 7(27%) and more than 600mg/m^2 in 4(15%) of patients. 15(72%) subjects were on weekly (day 1,8, and 15) schedule, 8 (31%) were on every 3 or 4 weeks and 3(12%) patients were on twice every 4 weeks. Three (12%) patients received irinotecan alone, 13(50%) and 10(38%) received irinotecan plus platinum and irinotecan plus other anticancer drugs, respectively. Grade 3 leukopenia was observed in 38 patients (32.2%) and grade four (severe) occurred in 9 patients (7.62%) who five of them also had grade 3-4 diarrhea concurrently (4.23%). Grade 4 or severe diarrhea was observed in three patients (2.54%) and grade 3 in 19 patients (16.1%). 16 of 22 patients with diarrhea, also experienced grade 3-4 leukopenia. Among them five patients who had both grade 4 leukopenia and grade ≥3 of diarrhea, two patients had UGT1A1*28 and UGT1A1*27 concurrently, two had heterozygous variant of UGT1A1*6, and one had none of the analyzed genotypes (homozygous for UGT1A1*1). It was proved that either heterozygous or homozygous for UGT1A1*28 is significant predictor for severe toxicity (odds ratio, 5.21; 95% CI, 1.98–13.96; P, 0.001). Conversely, there was no statistical significance between UGT1A1*6 with the occurrence of severe toxicity (odds ratio, 0.55; 95% CI, 0.15-1.61; P=0.2) [45] (See Table 1 and 2).

Korean population

In study by Kim et al., 50 patients were assessed for UGT1A1 genotypes (*28 and *6), and patients categorized into one of 3 groups based on the number of defective alleles (DA): 0 (wild type: *1/*1), 1 (containing only one of the *28 or *6 allele: *1/*28 or *1/*6), and 2 (*28/*28, *6/*6, or double heterozygous for *1/*28 and *1/*6). In the group with one DA (n=20, 40%), 14 (28%) and 6(12%) patients found to be heterozygous for UGT1A1*6 and *28, respectively. In the group with two DA (n=7, 14%), two patients (4%) simultaneously were heterozygous for UGT1A1*6 and *28, and three patients (6%) were homozygous for UGT1A1*6 and two (4%) patients for UGT1A1*28. Twenty tree patients (46%) had reference genotype and classified as 0 DA group. In this phase I dose escalating study, among 23 patients with metastatic colorectal cancer who received recommended doses of 200-350mg/m^2 of irinotecan on day 1 every 3 weeks with fixed-dose capecitabine; frequencies of grade 3-4 toxicities were: 26.1% for neutropenia (6/23), 17.4% for diarrhea (4/23), 8.7% for nausea (2/23) and 4.34% for each of febrile neutropenia, vomiting and asthenia (1/23). Grades 1-2 of these toxicities were as follows: neutropenia 30.43% (7/23), asthenia 69.56% (16/23), nausea 65.21% (15/23), vomiting 34.78% (8/23) and diarrhea 43.4% (10/23). Maximum of nine cycles were implemented. Grade 3-4 neutropenia and diarrhea observed in 9% and 18% of patient with zero defective allele and 50% and 25% in those with one defective allele. In those with two defective allele 25% experienced grade 3-4 neutropenia. While at the recommended dose level, the cumulative toxicities of patients in each genotype group did not vary significantly, neutropenia was mostly observed in the group of patients with one DA [46].

In a phase II trial by 30 included patients, 29 patients were assessed for genotype determination. The frequencies of the UGT1A1 *6 and *28 alleles were 15.5% and 10.3%, respectively, and none of these patients were homozygous for either UGT1A1*28 or

*6. Of the 29 patients, 17 (58.6%) had wild-type (*1/*1), 9 (31.0%) had one variant allele (*1/*2 8 or *1/*6), and 3 (10.3%) had two variant alleles (doubly heterozygous for *28 and *6). Thirty Korean patients received a total of 195 cycles of chemotherapy, irinotecan and S1 (IRIS regimen), for metastatic colorectal cancer. The most common grade 3 or 4 hematologic and non-hematologic toxicities were neutropenia (16/30, 53.4%) and diarrhea (5/30, 16.7%), respectively. Only in one patient, febrile neutropenia was reported (3.3%). Neutropenia grade 4, 3, 2 and 1 occurred in 5 (16.7%), 11 (36.7%), 8 (26.7%) and 3 (3%) of patients and Diarrhea of grade 4, 3, 2 and 1 was seen in 0, 5 (16.7%), 4 (13.4%) and 15 (50%) of patients respectively. Grade 3 of other toxicities including thrombocytopenia, anemia, stomatitis or enterocolitis occurred only in 1 of 30 patients (3.3%). Grade 3 of asthenia, anorexia and abdominal pain observed in 2(6.7%), 2(6.7%) and 3(10%) of patients. The incidence of grade 3/4 neutropenia in the three groups of patients, classified by the number of defective alleles they had; 0, 1, and 2 defective alleles, were 7/17, 6/9, and 3/3, respectively (p=0.043). Two of three patients who were double heterozygous for UGT1A1 *28 and *6, experienced grade 4 neutropenia [47].

In a study of 43 patients with advanced gastric cancer, UGT1A1 allele frequencies were 0.278 for *60, 0.222 for *6 and 0.095 for *28. Eleven patients (25%) had no defective allele. Fifteen patients (34.8%) with one defective allele included nine patients (21%) with *1/*60 and six patients (14%) with *1/*6 genotypes. In patients group of two defective alleles (13 patients, 30.2%); there were three patients (6.97%) with *60/*60, 1 patient (2.32%) with*6/*60, four patients (9.30%) with *6/*6 and five patients (11.62%) with*28/*60. No patients were homozygous for the *28 allele. Salvage therapy of these patients, included 250-500mg/m^2 irinotecan. Each patient received a median of four cycles. Grade 3-4 granulocytopenia was noted in 53.5% of patients (23/43), febrile neutropenia in 2/43 (4.6%), severe diarrhea in 4/43 (9.3%), fatigue in 32.6%, vomiting and nausea in 16.3% and anorexia in 14% of patients were occurred. Grade 3-4 neutropenia was observed in 9%, 46%, 57% and 100% of patients with zero, one, two and three defective alleles. Patient with no defective allele had a lower incidence of grade 3-4 neutropenia than other patients (p=0.018) [48] (See Table 1 and 2).

Chinese population

In a study included 41 patients for genotype assessment, 32 patients (80.0%) were homozygous wild-type and 8 (20.0%) were heterozygous for UGT1A1 *28. There was no reported homozygous variant genotype for UGT1A1* 28 in the study. Twenty patients (51.3%) had the homozygous wild-type, 18 patients (46.2%) were heterozygous, and 1 patient (2.6%) had the homozygous variant genotype for UGT1A1*6. Patients with advanced gastric cancer and esophageal-gastric carcinoma received two different doses of irinotecan (80 and 125mg/m^2) in day 1 every 14 days with cisplatin; following grade 3/4 toxicities were observed: Neutropenia 68.3% (28/41), leukopenia 39% (16/41), nausea 19.5% (8/41), anemia and thrombocytopenia 17.1% (7/41), vomiting and anorexia in 14.6% (6/41), febrile neutropenia 3/41) and diarrhea in 4.9% (2/41). The frequency of grade 3/4 of neutropenia was higher in the high-dose group (73.4%) compare with the low-dose group (65.4%). The occurrence of severe neutropenia was mostly reported in UGT1A1*28 heterozygotes (87.5%) than in UGT1A1*28 wild-type patients (65.6%), but did not reach a statistical significance level (p=0.396). No significant difference in grade 3/4 neutropenia was reported between UGT1A1 *6 wild-type and UGT-1A1 *6 variant genotypes (p=1.000). Additionally, grade 3/4 neutropenia were seen in 66.7% of wild-type patients, 75.0% of single defective allele patient, and 66.7% of two defective alleles patients (p=0.868) [49].

Gao et al. reported 276 patients who were classified as wild-type (with genotype: TA6/TA6 and GG, n=133, 48.2%), with single allele variants (with genotypes: TA6/TA6 and GA; or TA6/TA7 and GG; n=108, 39.1%), and two alleles variants (patients with genotypes: TA6/TA6 and AA; or TA6/TA7 and GA; or TA7/TA7 and GG; n=35, 12.7%). The frequencies of GG (wild), GA (heterozygous), AA (homozygous) genotypes for UGT1A1*6 were 64.5% (n=178), 28.6% (n=79), 6.9% (n=19) and TA6/TA6 (wild), TA6/TA7 (heterozygous), TA7/TA7 (homozygous) for UGT1A1*28 were 79.0% (n=218), 19.9% (n=55), 1.1% (n=3), respectively. Thirteen patients (4.7%) had double heterozygosity (GA concurrent with TA6/TA7). In 276 advanced colorectal cancer patients, following regimens and dose of irinotecan implemented: FOLFIRI (leucovorin calcium, 5-fluorouracil, and irinotecan) regimen (n=208, 180mg/m^2), irinotecan alone or plus cetuximab (n=52, 180mg/m^2), and irinotecan plus capecitabine (n=16, 180mg/m^2); Severe delayed-onset diarrhea observed in 16 patients (5.8%, 16/276) and 56 patients (20.3%, 56/276) developed severe neutropenia. No significant difference was reported between UGT1A1*28 and *6 and severe diarrhea (P=0.029 and 0.001, respectively). There was no significant difference for incidence of severe diarrhea in patients with different numbers of defective alleles, but patients with two alleles or single allele variants were more likely to develop severe neutropenia than wild-type patients (37.1 *vs*. 28.7% *vs*. 9.0%, P = 0.000) [50].

In a study in which 45 patients and 269 healthy subject of different three ethnicities; including 90 Chinese, 85 Malays and 94 Indians, were incorporated; 231 of 269 healthy Asians had reference genotype (85.7%), 35 healthy subjects were heterozygotes (13%) and three subjects were homozygotes (1.11%) for UGT1A1*6. In 266 subjects who were tested for UGT1A1*28, 161, 88 and 17 subjects had wild type (60%), heterozygotes (33%) and homozygotes (6.4%) genotype for UGT1A1*28 polymorphism. In 45 cancer patients 35 patients (77.7%) were wild type, eight (17.7%) and two (4.44%) patients were heterozygotes and homozygotes for UGT1A1*6, respectively. Thirty of 45 cancer patients had wild type genotype (66.6%) and 15 patients were heterozygotes (33.3%) while no one had homozygotes genotype of UGT1A1*28. In healthy Asian population study, three-to five-fold higher prevalence of UGT1A1*6 allele was observed in Chinese population compared with Malay and Indian populations. In this multi ethnicity (Chinese, Malays and Indians) study, 45 cancer patients received single agent irinotecan at 375mg/m^2 every 3 weeks. Neutropenia, leukopenia, thrombocytopenia, nausea and grade 0-2 diarrhea observed in 68% (29/45), 68.8% (31/45), 91.1% (41/45), 95.5% (43/45) and 86.6% (39/45) of patients respectively. Grade 3 of neutropenia occurred in 4/45 (8.1%) and grade 4 in 12/45 (24%) patients. Grade 3/4 leukocytopenia observed in 8/45 (17.7%) and 6/45 (13.3%) of patients respectively. Grade 3 of thrombocytopenia observed in 4/45 (8.8%), nausea 2/45 (4.4%) and diarrhea in 6/45 (13.3%) patients respectively. Severe grade 4 diarrhea was not occurred in the cancer patients. Of the six patients who experienced

grade 3 diarrhea, one patient had the homozygous UGT1A1*6 allele, one was a heterozygote (UGT1A1*1/*6) and four were the wild-type genotype. According to UGT1A1*28 genotypic status, there were two heterozygotes (UGT1A1*1/*28) and four wild-type genotype. They found that, mean Absolute Neutrophil Count (ANC) nadir values were independent of the UGT1A1*28 (P=0.300) genotype status. No patient who experienced grade 4 neutropenia were homozygous UGT1A1*28. Regarding to the UGT1A1*6 genotype status, eight of the patients who experienced grade 4 neutropenia were wild-type genotype, two patients were heterozygous and two patients were homozygous for the UGT1A1*6 allele. In patients who were homozygous of UGT1A1*6 allele, mean ANC value was 85% lower compared with patients with the reference genotype [33] (See Table 1 and 2).

American population

A study of 68 patients in Chicago who was in favor of ethnicity, 56 of them were white, nine were black and three were Hispanic; UGT1A1*28 genotype frequency evaluation revealed that 31 patients were wild-type (45.5%), 28 were heterozygotes (41.1%) and nine were homozygous (13.2%) for UGT1A1*28 genotype. In this single agent dose optimizing phase I study; irinotecan was administered every 3 weeks. Among patients, 30 patients had gastrointestinal cancers, 30 had lung and eight had other tumor types including breast, endocrine, thymic carcinoid, carcinoid, and maxillary sinus. The range of irinotecan administered doses to the patients ranged from 400 to 1,000mg. The predominant dose limiting toxicities was myelosuppression. It is noted that neutropenia was accounting for 75% of dose limiting toxicities (16 of 20) and severe diarrhea was accounting for 25% of it (five of 20). Patients with *1/*28 genotype tolerated 700mg (390mg/m^2), a dose higher than the standard 350mg/m^2. They also reported that patients with *1/*1 genotype could tolerate an even higher dose of 850mg (470mg/m^2) [51] (See Table 1 and 2).

Spanish population

In a study of 95 Spanish colorectal cancer patients, the allelic frequency of UGT1A1*28 in patients was analyzed and it was 0.34, within the range reported in Caucasian populations. In favor of genotype frequencies of *28; 42% of patients were with wild-type (40/95), 47.3% were heterozygotes (45/95) and 10.5% of patients were in homozygote group (10/95). In these patients different regimens with different dose of irinotecan implemented: A) irinotecan alone 350mg/m^2 every 3 weeks, B) irinotecan 350mg/m^2 every 3 weeks plus Raltitrexed, C) irinotecan 80mg/m^2 every 2 weeks plus a dose of 2250mgm^2 of 5- Fluorouracil (5-FU) in every cycle and D) irinotecan 180mg/m^2 every 2 weeks plus 5-FU and leucovorin. These grade 3-4 toxicities were obtained in all patients: diarrhea 30.5% (29/95), asthenia 35.8% (34/95), neutropenia 21% (20/95), nausea 18% (17/95) and infection 8.4% (8/95). In total, 55 patients (58%) experienced some kind of grade 3/4 adverse effect and 28 out of these patients (48%) developed more than two of grade 3/4 toxicities. In patients with wild-type genotype 17% and 15% experienced diarrhea and hematological toxicity including grade 3/4 neutropenia. Diarrhea and hematological toxicity were observed in 33% and 27% among heterozygous and 70% and 40% among homozygous, respectively. There was a marked relationship between the appearance of severe diarrhea (P=0.005) and the heterozygous and homozygous UGT1A1*28 polymorphism. The only variable that significantly predicted the appearance of severe diarrhea was UGT1A1 genotype [52] (See Table 1 and 2).

Saudi Arabia population

Alkharfy et al. conducted a genotyping study on 192 apparently healthy unrelated Saudi male volunteers (20-25 years old) of different geographic regions. Among them, UGT1A1*60; 20 subjects (10.6%) were wild type while 67(35.4%) and 102 (54%) had homozygotes and heterozygotes, respectively. Nighty four (50%) of subjects were wild-type for UGT1A1*28, 90 (47.9%) were heterozygotes for *28, 3 (1.4%) and 1 (0.5%) were homozygotes for *28 and *37, respectively. All of the subjects had wild-type genotype for UGT1A1 *6 and *27 polymorphisms. Frequency of reference allele and mutant allele was 37.6% and 62.4% for *60 polymorphism, 74.3% and 25.7% for *28 polymorphism and 0.5% for mutant allele of *37 polymorphism. Subjects from the eastern region mostly indicated a UGT1A1*60 mutant allele, whereas this mutation was found in about 58-68% in other regions. In similar manner, the UGT1A1*28 wild genotype was reported least often in eastern Saudis (36%) and highest in those of northern descent (58%). Among all recruited population, only one subject from the western region carries UGT1A1*37; likewise, the UGT1A1*36 was not present in the studied population [53] (See Table 1 and 2).

Iranian population

There is a published data over Iranian population in which 300 unrelated healthy individuals, including most ethnicities, Persian, Azari, Lure, Kurdish, Arab, Baluch and Caspian were recruited. Frequency distribution of the UGT1A1 *6 (G/G, A/G, A/A) genotype was analyzed. It was revealed that the frequencies of A/G and A/A were 13% and 0.33%; respectively. In Iranian population the allele frequency of G (93.16%) was significantly ($p<0.0001$) higher than A (6.83%).The genotype frequencies of the homozygous (A/A), heterozygous (A/G) and wild-type (G/G) variants of UGT1A1 *6 were also significantly different ($p < 0.0001$) in all Iranian ethnic groups. The frequency of the wild-type (G/G) variant of UGT1A1 *6 was highest in Caspians (100%), and lowest in Bluchs (80%). Only in the Persian ethnicity, homozygous (A/A) variant of UGT1A1*6 was observed, while it was not detected in the Lure, Azari, Bluch, Kurdish, Caspian and Arab ethnicities. The frequency of the heterozygous (A/G) variant of UGT1A1*6 was significantly higher in the Bluch ethnic group (20%) and in the Persian (15.69%) ethnic group ($p<0.00001$). The results showed that the frequency of the homozygous (A/A) variant of UGT1A1*6 was observed in central Iran, while no frequency was reported in south, north, west and east of Iran, indicating an insignificant contribution of this genotype in Iranian population. In the center of Iran heterozygous (A/G) variant of the UGT1A1*6 frequency was the highest [54] (See Table 1 and 2).

Toxicity results of 70 evaluated cases of cancer patients received irinotecan in our institute, showed that less than 9% have been affected by irinotecan-induced diarrhea and more than 20% experienced neutropenia in regular dose of 100mg/m^2.

Discussion

In this review, we tried to obtain all published data, however the emphasizing was on Asian population due to paucity of data in other population. By overviewing all mentioned data, we concluded that in non-Asian population studies consisted of white, black and Hispanic

ethnicities and Spanish patients (68 and 95 patients); as in most other studies, prevalence of UGT1A1*28 was approximately as high as 45% for heterozygous and 12% for homozygous polymorphism [50,51]. On the other hand, in Asian population, UGT1A1 *28 allele was most prevalent in Saudi, Thai and Korean population with reported values of 25.7%, 12.5% and 10.3%, respectively [35,47,53].

It is reported that maximum reported frequency of *6 allele was for a Korean study [47], whilst, no allele *6 reported in Saudi population [53].

UGT1A1*28 heterozygous genotype was most frequent in Saudi population (47.9%) [53] that is comparable to values reported in non-Asian studies [51,52]. The least frequency reported was 8% in a Chinese study [49]. Other Asian studies revealed prevalence of 11% to 33% [47-49].

Homozygous UGT1A1*28 was most prevalent in an Asian multi-ethnicity study (6.4%) [33], however, in a Japanese [43] and a Chinese [49] study no homozygous of *28 have been reported. Other UGT 1A1 *28*28 prevalence were reported in a range between 1.1 to 4% [35,36].

Maximum prevalence of *6 heterozygous in reviewed studies was in the Chinese population [49] with a value of 46.2% and the minimum value was 10.6% in the Japanese study [45]. Other frequencies were 13% till 30% [36,38].

Homozygous UGT1A1*6 was not seen in the Thai [35] and the Japanese [43] study. The most prevalent was for the Korean study [48] with 9.3% and the Chinese study with a 6.9% frequency [50]. In the Iranian study, the least prevalence was reported [54]. Other reports were between 1.1% and 6% [55].

As combined frequency of UGT1A1*6 and *28; the Japanese study reported 11.1% as the maximum frequency for homozygous [38]. In the Japanese and Korean population there was no homozygous genes [43,47]. Other studies revealed between 4.5-10% prevalence [39,50]. Frequency of both UGT1A1*28 and *6 was most prevalent in a Chinese study with 54.2% [49] and other reported frequencies were between 29.6-51.4% [36,38].

Presence of UGT1A1*28 and *6 concurrently in subjects was mostly reported in the Korean study (12%) (47). Other reported frequencies ranged from 3% to 5.5%. In three studies, frequency of UGT1A1*60 evaluated and a marked difference between the Korean and Japanese studies and the Saudi population; 6.97 and 8% *vs.* 35.4% in homozygous genotype and 21 and 38.7% *vs.* 54% in heterozygous genotype, respectively was seen [43,48,53]. No variant allele of UGT1A1 *27 was reported in the Saudi population while heterozygous of *27 in the Japanese population was 2.7% [40,53].

Of reported severe (grade 4-3) neutropenia, the study of 27 Japanese patients showed the most frequency (89%) [37]. The Thai population study with 44 patients reported the least frequency of sever neutropenia (6.8%) [35]. Other reported frequencies were in the range of 10.7% to 8.3%. The prevalence of neutropenia was as high as 22% of all recruited patients in our oncology center as well [36,38].

Between Asian studies, severe diarrhea was reported as maximum frequency of 18.5% in the Japanese study of 118 patients [45] and as minimum frequency of 2.7% in the study of 75 Japanese patients [40]. A range of 4.1 to 17.4% was reported in other studies [37-39].

In the study conducted in Barcelona with 95 patients, prevalence of severe neutropenia was 21% and for severe diarrhea was 30.5% [52]. The prevalence of diarrhea was as similar as some other Asian studies [41,48].

In the majority of reviewed studies, a significant association was revealed between presence of genotype UGT1A1*28 or *6 in form of either heterozygous or homozygous and incidence of severe adverse effects. However, in a study of 21 patients in Japan no significant relation was seen between polymorphism and severe diarrhea and neutropenia [39]. In a Chinese study of 276 patients, UGT 1A1*6 and *28 was significantly associated with incidence of severe neutropenia but not with severe diarrhea [50].

In a study of 28 Japanese subjects, less toxicity of grade 4-3 observed in patients with mutant allele *28 *vs.* wild type [41].

In the single polymorphism evaluation study implemented in 300 Iranian subjects in which only UGT1A1*6 genotype was assessed, The prevalence of heterozygous and homozygous genotypes was reported 13% and 0.33%, respectively [54]. Due to lower prevalence of UGT 1A1*6 genotypes in comparison with other Asian population and considerable frequency of UGT1A1*28 in Saudi and Thai subjects *vs.* other Asian population; we suggest evaluation of *28 allele prevalence. The Iranian population in future polymorphism studies. According to Asian studies in which a significant association was found between adverse effects of grade 3-4 and UGT1A1* 28 and *6 genotypes, for an optimum therapy, we recommend analysis of UGT1A1 polymorphism before initiating treatment modalities contain irinotecan. In Iranian population, in comparison with UGT1A1*28 genotype, the prevalence of UGT1A1*6 genotype is mostly evaluated, while the prevalence was lower among all other Asian countries. The prevalence of UGT1A1*28 and *6 genotypes was different among Asian countries in comparison with western countries and it is even differ between Asian countries. Furthermore, the differences might be induced the potential of irinotecan's adverse effects in different grade and potency.

Conclusion

Our results confirmed the possible association of irinotecan related adverse effects and different polymorphisms of the UGT 1A1 enzyme. In different settings, the frequency of the adverse effects varies substantially. Hence, clinicians should consider these variations and adapt patients' treatment strategy based on toxicity reports of related geographical location. Surly, ethnicity is a determining issue for occurrence of irinotecan associated adverse effects.

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