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ORIGINAL ARTICLE

Coadministration of cytotoxic chemotherapeutic agents with irinotecan is a risk factor for irinotecan-induced cholinergic syndrome in Japanese patients with cancer

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Abstract

Background Cholinergic syndrome is an acute adverse event frequently observed in patients administered irinotecan, and can sometimes negatively affect their quality of life. In some manifestations of the syndrome such as bradycardia, careful monitoring of patients is advised. In this study, we retrospectively investigated the risk factors associated with irinotecan-induced cholinergic syndrome in Japanese patients with cancer.

Methods Patients who received irinotecan-based chemotherapy between April 2014 and June 2018 were examined. Patient backgrounds and clinical data during the first cycle of an irinotecan-containing regimen, including cholinergic syndrome manifestation within 24 h after the start of treatment, were collected from medical records. Univariate and multivariate analyses were performed to assess the risk of irinotecan-induced cholinergic syndrome.

Results Among 179 patients administered an irinotecan-containing regimen, 51 experienced cholinergic syndrome after the initiation of treatment. The most common symptom was sweating followed by diarrhea, abdominal pain, lacrimation, and nasal discharge. 42 patients developed symptoms of cholinergic syndrome during their first treatment with irinotecan. Multivariate analyses revealed that the incidences of cholinergic syndrome in patients administered 2 or 3 chemotherapeutic agents; i.e., irinotecan plus 1 or 2 other cytotoxic anticancer drug(s), were significantly higher than that in patients administered irinotecan alone [odds ratio (OR) 4.35, 95% confidence interval (CI) 1.5–12, $p=0.0053$ and OR 4.50, 95% CI 1.5–14, $p=0.0093$, respectively]. The addition of a molecularly targeted drug did not affect the incidence of cholinergic syndrome.

Conclusion The incidence rate of irinotecan-induced cholinergic syndrome increased concomitantly with the addition of cytotoxic chemotherapeutic agents administered.

Keywords Adverse events · Chemotherapeutic agents · Cholinergic syndrome · Irinotecan · Risk factors

Introduction

Irinotecan hydrochloride is a topoisomerase I inhibitor that is used worldwide as a treatment for many solid tumors, including metastatic colorectal cancer [1]. However, this anticancer drug can cause severe, potentially fatal toxicities such as neutropenia and/or delayed diarrhea [2–6].

Irinotecan is a prodrug that is extensively metabolized in the liver to produce the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) by carboxylesterase, and is then conjugated predominantly by liver UDP-glucuronosyltransferase (UGT) 1A1 to form inactive SN-38 glucuronide (SN-38G) [2]. The *UGT1A1*28* and **6* polymorphisms in the *UGT1A1* gene can decrease the expression of the UGT1A1 enzyme and reduce its catalytic activity, respectively, resulting in

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significantly decreased conversion of SN-38 to SN-38G. Therefore, patients who carry the *UGT1A1*6/*6*, **28/*28*, or **6/*28* genotypes show severe irinotecan-induced neutropenia, in contrast to those carrying *UGT1A1*1/*1*, **1/*6*, or **1/*28* [3–6]. In addition to severe neutropenia and/or delayed diarrhea [2–6], 'cholinergic syndrome', is another acute adverse event that is frequently observed after commencing irinotecan treatment.

Symptoms of cholinergic syndrome include abdominal pain, bradycardia, diarrhea, lacrimation, sweating, and/or nasal discharge; these conditions often lower the patients' quality of life (QOL) [7–10]. Miya et al. [8] reported a patient with recurrent colorectal cancer who experienced repeated bradycardia after irinotecan treatment, and recommended careful monitoring for cholinergic syndrome manifestations such as bradycardia as well as severe hematologic toxicity and/or diarrhea during irinotecan-containing chemotherapy. Fujii et al. [9] recently reported a significant association between the occurrence of irinotecan-related cholinergic syndrome and improved overall survival in patients with colorectal cancer. Irinotecan-induced cholinergic syndrome also tended to show a positive correlation with progression-free survival. Nonetheless, there have been few investigations to identify the risk factors for the development of irinotecan-induced cholinergic syndrome.

Among Western patients, the incidence of irinotecan-induced cholinergic syndrome is higher in patients administered irinotecan doses of 250–350 mg/m^2 than in those administered 150 mg/m^2 [11–14]. On the other hand, the effects of irinotecan dose on the incidence and/or severity of cholinergic syndrome among Japanese patients remains unclear. Irinotecan is frequently administered to cancer patients as a combination therapy with other cytotoxic chemotherapeutic agents such as 5-fluorouracil (5-FU), cisplatin, and oxaliplatin [15–18]. Furthermore, molecularly targeted drugs including aflibercept beta, bevacizumab, cetuximab, panitumumab, and ramucirumab have simultaneously been administered to patients with irinotecan-containing chemotherapy [19–23]. However, the combinatorial effects of chemotherapeutic agents and/or molecularly targeted drugs on irinotecan-induced cholinergic syndrome remain unclear, and the risk factors for irinotecan-related cholinergic syndrome have not been fully identified to date.

Based on this background, we retrospectively examined the clinical factors related to the onset and incidence of irinotecan-related cholinergic syndrome in patients with cancer who received irinotecan-containing regimens via their medical records.

Patients and methods

Study design

This retrospective study was performed at Showa University Hospital. All Japanese patients with cancer who received their first cycle of an irinotecan-based regimen between April 2014 and June 2018 were included in this investigation to identify the clinical factors associated with irinotecan-related cholinergic syndrome. This study was approved by the Institutional Review Board of Showa University (Approval Number 2181).

Patients

All patients, who were managed by medical oncologists at our department, were 20 years or older, had histologically confirmed solid tumors, and were genotyped for *UGT1A1*6* and **28*. These patients were administered irinotecan monotherapy or a combination of irinotecan and other cytotoxic chemotherapeutic agents. Some, but not all patients were also administered a molecularly targeted drug. Patients who had previously received any irinotecan-containing chemotherapy or had been started on any irinotecan-containing chemotherapy regimen in any other hospital were excluded.

Chemotherapeutic regimens containing irinotecan

The irinotecan-containing regimens administered to patients were as follows: (1) One cytotoxic chemotherapeutic agent, irinotecan monotherapy involving irinotecan hydrochloride at a dose of 100 mg/m^2 as a 90 min intravenous (i.v.) infusion on days 1, 8, and 15 repeated every 4 weeks [24], or irinotecan hydrochloride at a dose of 150 mg/m^2 as a 90 min i.v. infusion on day 1 repeated every 2 weeks [25, 26]. (2) Two cytotoxic chemotherapeutic agents involving (i) FOLFIRI, irinotecan hydrochloride at a dose of 150 mg/m^2 as a 90-min i.v. infusion, *l*-leucovorin (*l*-LV) at a dose of 200 mg/m^2 as a 2 h i.v. infusion followed by 5-FU 400 mg/m^2 as an i.v. bolus then by 2400 mg/m^2 as a 46 h continuous i.v. infusion, all administered on day 1 and repeated every 2 weeks [15]; (ii) irinotecan and cisplatin, irinotecan hydrochloride at a dose of 60 mg/m^2 as a 90 min i.v. infusion on days 1, 8, and 15 plus cisplatin at a dose of 60 mg/m^2 on day 1, repeated every 4 weeks [16]; (iii) IRIS, irinotecan hydrochloride at a dose of 150 mg/m^2 as a 90 min i.v. infusion on day 1 followed by S-1 (tegafur, gimeracil, and oteracil potassium) 80 mg/day for body surface areas (BSAs) < 1.25 m^2, 100 mg/day for 1.25 ≤ BSAs < 1.50 m^2, and 120 mg/day for BSAs ≥ 1.50 m^2 for 2 weeks orally, repeated every 4 weeks [27]. (3) Three cytotoxic chemotherapeutic agents involving

(i) modified FOLFIRINOX (mFOLFIRINOX), oxaliplatin at a dose of 85 mg/m^2 as a 2 h i.v. infusion where *l*-LV was administered at a dose of 200 mg/m^2 as a 2 h i.v. infusion, irinotecan hydrochloride at a dose of 150 mg/m^2 as a 90 min i.v. infusion, followed by 5-FU 2400 mg/m^2 as a 46 h continuous i.v. infusion, all administered on day 1 and repeated every 2 weeks [17]; (ii) modified FOLFOXIRI (mFOLFOXIRI), irinotecan hydrochloride at a dose of 150 mg/m^2 as a 90 min i.v. infusion, *l*-LV was administered at a dose of 200 mg/m^2 as a 2 h i.v. infusion, oxaliplatin 85 mg/m^2 as a 2 h i.v. infusion followed by 5-FU 2400 mg/m^2 as a 46 h continuous i.v. infusion, all administered on day 1 and repeated every 2 weeks [18].

Data collection

Patient background data such as sex, age, type of cancer, Eastern Cooperative Oncology Group performance status, and smoking history, as well as irinotecan-containing chemotherapy-related data including laboratory tests and the onset of symptoms of cholinergic syndrome (abdominal pain, bradycardia, diarrhea, lacrimation, nasal discharge, and/or sweating) within 24 h after the start of treatment were collected for all patients from the medical records, during the entire period of irinotecan-containing chemotherapy. All symptoms of cholinergic syndrome were judged by medical oncologists who treated the patients with an irinotecan-containing regimen. The severity of cholinergic syndrome was not noted because these data were not necessarily described in the medical records. If an anticholinergic drug was prescribed to treat a cholinergic syndrome-related symptom, that information was also collected.

Statistical analyses

Differences in qualitative variables were tested using Fisher's exact test or Pearson's Chi-square test. Logistic regression analysis was performed for the multivariate analysis. Two-tailed p values less than 0.05 were considered statistically significant. All analyses were performed using the JMP software, version 13.0 (SAS Institute, Cary, NC).

Results

Patient characteristics

During the study period, 194 patients with cancer received irinotecan-containing chemotherapy. 15 patients were excluded from the analyses: two patients who commenced an irinotecan-containing chemotherapy in other hospitals, ten who previously received irinotecan-containing chemotherapy, two without information on their *UGT1A1* genotype, and one younger than 20 years old. Hence, 179 patients were ultimately analyzed. The characteristics of the patients in our study are shown in Table 1.

Treatment of patients

The irinotecan-containing regimens administered to the patients are summarized in Table 2. 91 patients (51%) received 1 cytotoxic chemotherapeutic agent (irinotecan monotherapy, with or without a molecularly targeted drug). Regimens with a combination of 2 cytotoxic chemotherapeutic agents (FOLFIRI, irinotecan and cisplatin, or IRIS, with or without a molecularly targeted drug) were administered to 66 patients (37%). 22 patients (12%) received 3 cytotoxic chemotherapeutic agents (mFOLFIRINOX or mFOLFOXIRI, with or without a molecularly targeted drug). Molecularly targeted drugs were administered to 57 patients (32%). The median dose of irinotecan was 150 mg/m^2, which was equivalent to 210 mg/body.

Table 1 Patient characteristics

Characteristics	Patient number[a]
Sex	
Female/male	70/109
Age (years)	
Median (range)	65 (26–85)
Type of cancer	
Colon	90
Lung	28
Gastric	27
Pancreas	9
Others	25
Performance status score	
0	42
1	121
2	13
3	3
UGT1A1 genotype	
**1/*1*	104
**1/*6*, or **1/*28*	60
**6/*6*, **28/*28*, or **6/*28*	15
Creatinine clearance (Ccr) (mL/min) [b]	
≥ 60/< 60	139/40
Smoking	
Never/former/current	72/93/14

[a]Total patient number was 179

[b]Ccr (mL/min) = [140 − age (years) × body weight (kg)]/72/serum creatinine (mg/dL), Ccr in women was calculated by multiplying the value obtained using this equation by 0.85

Table 2 Treatment regimen in patients

Treatment	Patient number (total = 179)
Regimen	
One cytotoxic chemotherapeutic agent	
Irinotecan (plus panitumumab)	91 (3)
Two cytotoxic chemotherapeutic agents	
FOLFIRI[a] (plus bevacizumab, cetuximab, panitumumab or ramucirumab)	62 (30, 9, 5, or 3)
Irinotecan and cisplatin	3
IRIS[b] (plus bevacizumab)	1 (1)
Three cytotoxic chemotherapeutic agents	
mFOLFIRINOX[c]	12
mFOLFOXIRI[d] (plus bevacizumab)	10 (6)
Molecularly targeted drug used in irinotecan-containing regimens	
Bevacizumab	37
Cetuximab	9
Panitumumab	8
Ramucirumab	3
Dose of irinotecan (mg/m^2)	
Median (range)	150 (60–150)
Dose of irinotecan (mg/body)	
Median (range)	210 (80–290)

[a]FOLFIRI: irinotecan, *l*-leucovorin (*l*-LV), bolus 5-fluorouracil (5-FU), and infusional 5-FU

[b]IRIS: irinotecan, and S-1 (tegafur, gimeracil, and oteracil potassium)

[c]mFOLFIRINOX: oxaliplatin, irinotecan, *l*-LV, and infusional 5-FU

[d]mFOLFOXIRI: irinotecan, oxaliplatin, *l*-LV, and infusional 5-FU

Cholinergic syndrome manifestation

The symptoms of cholinergic syndrome observed in our patients are shown in Table 3. Among the 179 patients treated with irinotecan-containing regimens, 51 experienced symptoms consistent with cholinergic syndrome following treatment; the most common was sweating ($n = 31$). Ten patients experienced sweating and diarrhea simultaneously, and 5 experienced both diarrhea and abdominal pain. Among the 51 patients, 42 (82%) developed cholinergic syndrome at their initial treatment with an irinotecan-containing regimen, whereas others developed the syndrome at second treatment or later.

27 patients (53%) received the anticholinergic drug to treat their irinotecan-induced cholinergic syndrome. Among those who developed cholinergic syndrome, approximately half were administered prophylactic anticholinergic drug before their subsequent treatment. 26 of the 27 patients (96%) did not experience the irinotecan-induced cholinergic syndrome after receiving prophylactic anticholinergic treatment, emphasizing the effectiveness of the prophylactic anticholinergics.

Table 3 Summary of cholinergic syndrome manifestations in the patients

Cholinergic syndrome	Number of patients
Symptoms[a]	
Sweating	31
Diarrhea	20
Abdominal pain	15
Nasal discharge	3
Lacrimation	3
Onset of symptoms	
First treatment	42
Second treatment or later	9
Treatment of symptoms with the anticholinergic drug[b]	
No	24
Yes	27
Prophylactic administration of the anticholinergic drug before the subsequent treatment[c]	
No	19
Yes	27

[a]The total number of patients who experienced cholinergic syndrome was 51. Some patients showed multiple syndromes

[b]All anticholinergic drugs administered were scopolamine butylbromide

[c]26 patients were administered scopolamine butylbromide, and one received atropine

Risk factors for cholinergic syndrome

We first performed univariate analysis to identify clinical factors associated with irinotecan-induced cholinergic syndrome (Table 4). The number of cytotoxic chemotherapeutic agents was significantly related to the incidence of cholinergic syndrome ($p < 0.05$, Pearson's Chi-square test); the incidences in patients receiving 1, 2, and 3 cytotoxic chemotherapeutic agent(s) were 17.6%, 37.9%, and 45.5%, respectively. The Cochran-Armitage trend test revealed that the higher the number of cytotoxic chemotherapeutic drugs, the greater the incidences of irinotecan-related cholinergic syndrome ($p < 0.05$). However, the addition of a molecularly targeted drug did not affect the incidence of cholinergic syndrome. As shown in Table 4, the remaining investigated clinical factors were not associated with the incidence of cholinergic syndrome.

The results of multivariate analysis are shown in Table 5. The incidence of cholinergic syndrome in patients who received two cytotoxic chemotherapeutic agents (FOLFIRI, irinotecan and cisplatin or IRIS) was significantly higher than that in patients who received 1 cytotoxic

Table 4 Univariate analysis of potential risk factors for cholinergic syndrome

Factors	Patients with cholinergic syndrome ($n=51$)	Patients without cholinergic syndrome ($n=128$)	p value
Sex			
Female	18	52	0.61[†]
Male	33	76	
Age (years)			
< 75	43	106	1.0[†]
≥ 75	8	22	
Performance status score			
< 2	44	119	0.16[†]
≥ 2	7	9	
UGT1A1 genotype			
**1/*1*	33	71	0.31[‡]
**1/*6* or **1/*28*	16	44	
**6/*6*, **28/*28* or **6/*28*	2	13	
Creatinine clearance (Ccr) (mL/min)[d]			
≥ 60	40	99	1.0[†]
< 60	11	29	
Smoking			
Never	20	52	0.98[‡]
Former	27	66	
Current	4	10	
Number of cytotoxic chemotherapeutic agent(s) in a regimen			
1[a]	16	75	0.0036[‡]
2[b]	25	41	0.0011[§]
3[c]	10	12	
Molecularly targeted drug			
No	32	90	0.38[†]
Yes	19	38	
Dose of irinotecan (mg/m^2)			
< 150	14	53	0.090[†]
150	37	75	

[†]Fisher's exact test

[‡]Pearson's Chi-square test

[§]Cochran-Armitage trend test

[a]Irinotecan

[b]FOLFIRI, irinotecan and cisplatin, or IRIS

[c]mFOLFIRINOX or mFOLFOXIRI

[d]Ccr (mL/min) = [140 − age (years) × body weight (kg)]/72/serum creatinine (mg/dL), Ccr in women was calculated by multiplying the value obtained using this equation by 0.85

chemotherapeutic agent (irinotecan monotherapy) [odds ratio (OR) 4.35, 95% confidence interval (CI) 1.5–12, $p=0.0053$]. A significantly higher incidence rate of cholinergic syndrome was observed in patients who received three cytotoxic chemotherapeutic agents (mFOLFIRINOX or mFOLFOXIRI) than in those who received irinotecan monotherapy (OR 4.50, 95% CI 1.5–14, $p=0.0093$). These results indicate a positive correlation between the addition of cytotoxic chemotherapeutic agents administered as part of irinotecan-containing regimens and the incidence of irinotecan-induced cholinergic syndrome.

Discussion

We found a positive correlation between the addition of cytotoxic chemotherapeutic agents in administered irinotecan-containing regimen and the incidence of cholinergic

Table 5 Multivariate logistic regression analysis of potential risk factors for cholinergic syndrome

Factors	OR	95% CI	*p* value[†]
Sex			
Male	Reference		
Female	1.03	0.43–2.5	0.95
Age (years)			
< 75	Reference		
≥ 75	1.29	0.46–3.6	0.63
Performance status score			
< 2	Reference		
≥ 2	3.27	0.99–11	0.053
UGT1A1 genotype			
**1/*1*	Reference		
**1/*6* or **1/*28*	0.736	0.34–1.6	0.44
**6/*6*, **28/*28* or **6/*28*	0.333	0.058–1.9	0.22
Creatinine clearance (Ccr) (mL/min)[d]			
≥ 60	Reference		
< 60	1.04	0.42–2.6	0.93
Smoking			
Never	Reference		
Former	1.25	0.52–3.0	0.62
Current	1.24	0.28–5.5	0.77
Number of cytotoxic chemotherapeutic agents in a regimen			
1[a]	Reference		
2[b] versus 1	4.35	1.5–12	0.0053
3[c] versus 1	4.50	1.5–14	0.0093
Molecularly targeted drug			
No	Reference		
Yes	0.54	0.20–1.4	0.22
Dose of irinotecan (mg/m^2)			
< 150	Reference		
150	1.23	0.48–3.1	0.67

OR odds ratio; *CI* confidence interval

[†]Chi-square test

[a]Irinotecan

[b]FOLFIRI, irinotecan, and cisplatin; or IRIS

[c]mFOLFIRINOX or mFOLFOXIRI

[d]Ccr (mL/min) = [140 − age (years) × body weight (kg)]/72/serum creatinine (mg/dL), Ccr in women was calculated by multiplying the value obtained using this equation by 0.85

syndrome. The incidence rate of cholinergic syndrome in patients administered 2–3 cytotoxic chemotherapeutic agents was significantly higher than that in patients administered irinotecan monotherapy (Table 5). At present, the mechanism through which cytotoxic chemotherapeutic agents had an additive effect when combined with irinotecan monotherapy to produce cholinergic syndrome remains unclear. Valencak et al. [28] reported a 53-year-old woman who experienced cholinergic syndrome attributable to irinotecan therapy; her regimen comprised 85 mg/m^2 oxaliplatin on days 1 and 15 followed by 80 mg/m^2 irinotecan on days 1, 8, and 15. The patient complained of hypersalivation and abdominal pain along with decreased blood pressure immediately after the first infusion of irinotecan. Interestingly, she did not experience these side effects with the second dose of irinotecan alone on day 8; however, on day 15, her symptoms promptly recurred during the infusion of irinotecan following oxaliplatin administration. After this second episode, the regimen was modified, and oxaliplatin was infused on days 1 and 14 while irinotecan was administered separately on days 2, 8, and 15. The second cycle of treatment with this split schedule was tolerated without any side effects, and the patient did not experience any irinotecan-induced acute symptoms with this modified regimen. However, when the patient was re-challenged with the original schedule of both drugs administered on the same day, she again experienced symptoms consistent with cholinergic syndrome. These results suggest that the irinotecan-induced cholinergic syndrome was triggered by the coadministration of oxaliplatin, as the adverse effect was not observed with the application of irinotecan alone. Taken together, the coadministration of oxaliplatin may be, at least in part, responsible for the significantly higher incidence of irinotecan-induced cholinergic syndrome observed in patients administered three cytotoxic chemotherapeutic agents, including oxaliplatin, than that in patients treated with irinotecan alone. On the other hand, there have been no reports of higher incidences of irinotecan-related cholinergic syndrome in patients coadministered 5-FU. Further studies are, therefore, warranted to clarify the mechanisms responsible for the additive effects of cytotoxic chemotherapeutic agents on the incidence of irinotecan-induced cholinergic syndrome.

In general, irinotecan-induced cholinergic syndrome impairs the patients' QOL. Medical oncologists sometimes treat such patients with anticholinergic drugs either to improve their QOL or to prophylactically prevent the development of symptoms in subsequent treatments with irinotecan, nonetheless there are no sufficient lines of evidence for the use of such anticholinergics to treat cholinergic syndrome [7, 8, 10, 29–31]. Our present results suggest that appropriate anticholinergic usage should be established for patients who will require irinotecan combined with other cytotoxic chemotherapeutic agents.

Irinotecan-related cholinergic syndrome is observed at various doses of irinotecan, and its incidence rate appears to be dose-dependent [11–14]. We summarized the relationship between the incidence rate of irinotecan-induced cholinergic syndrome and doses in patients administered irinotecan monotherapy in previous studies [11–14] as well as ours in Table 6. We found that patient groups administered irinotecan doses of 250 mg/m^2 or greater

Table 6 Relationship between irinotecan dose and the incidence of cholinergic syndrome

Dose of irinotecan (mg/m^2)			References
< 150	150–249	≥ 250	
21% (60–100)	33% (150)		Current study
41% (125)		61% (250), 68% (350)	Schoemaker et al. [14]
	19% (175)	53% (350)	Tsavaris et al. [13]
		56% (250)	Blandizzi et al. [12]
	33% (240)	83% (340)	Pitot et al. [11]

Numbers in parentheses indicate the dose of irinotecan. The incidences of cholinergic syndrome in studies with irinotecan monotherapy were compared

had higher incidences of cholinergic syndrome (> 50%), whereas those receiving irinotecan doses less than 250 mg/m^2 had lower incidence rates (approximately 40% or less). In our present study, the incidence rates of cholinergic syndrome were 33% at an irinotecan dose of 150 mg/m^2 and 21% at doses under 150 mg/m^2, which were approximately consistent with the values observed in previous studies (Table 6). There was no significant difference in the incidence rates between the < 150 and 150 mg/m^2 dosage groups, indicating that dose-dependent increases of cholinergic syndrome were not observed at irinotecan doses ≤ 150 mg/m^2. Hence, the incidence of irinotecan-induced cholinergic syndrome appears to increase at doses higher than 250 mg/m^2. On the other hand, Kanbayashi et al. [10] recently reported that irinotecan dose (mg/body) was a significant factor for the development of cholinergic syndrome, although we did not observe a significant relationship between cholinergic syndrome and irinotecan dose [median 210 (range 80–290) mg/body (Table 2)] (data not shown). Further studies are necessary to clarify the effects of irinotecan dose on the onset of cholinergic syndrome.

Several lines of evidence have linked *UGT1A1*28* and *UGT1A1*6* genotypes to irinotecan-induced toxicity, especially severe neutropenia [3–6], because the $(TA)_7$ allele in the proximal promoter region of *UGT1A1* (*UGT1A1*28*) [32] as well as a mutation in exon 1 (211G < A, G71R), referred to as *UGT1A1*6* [32], can cause reduced gene expression and decreased catalytic activity of the drug-metabolizing enzyme, respectively, resulting in a significantly decreased conversion rate of SN-38 to SN-38G [3–6]. Our current data revealed no significant association between the *UGT1A1* genotypes and irinotecan-induced cholinergic syndrome, suggesting that plasma levels of SN-38 and SN-38G played no role in the occurrence of cholinergic syndrome, which is consistent with the results obtained by Blandizzi C et al. [33].

The incidence of irinotecan-induced cholinergic syndrome appears to be roughly similar between Japanese (current study) and Western patients [11–14], when patients were treated with irinotecan doses less than 250 mg/m^2 (Table 6). The frequency of Japanese patients with two 'risk alleles' (i.e., *UGT1A1*28/*28*, **6/*6*, and **6/*28*) (10.1%) [34] was almost equal to that of Western patients with the risk allele *UGT1A1*28/*28* (~ 11%) [35]. In addition, our current data showed no significant association between the *UGT1A1* genotypes and the cholinergic syndrome at irinotecan doses of ≤ 150 mg/m^2 (Table 4). Overall, the incidence of irinotecan-induced cholinergic syndrome in Japanese and Western patients might be almost similar at least with irinotecan doses less than 250 mg/m^2, and is not related to *UGT1A1* genotypes.

Approximately 20% of patients examined in this study showed a Ccr < 60 mL/min (Ccr median 75 mL/min, range 20–199 mL/min), and there was no correlation between renal function and irinotecan-related cholinergic syndrome. de Jong et al. [36] demonstrated that irinotecan clearance observed in patients with mild renal failure (Ccr 35–66 mL/min) was slightly lower than that in patients with normal renal function (Ccr > 98 mL/min), although clearances of SN-38 and SN-38G did not differ substantially. However, patients in our study who had Ccr levels < 60 mL/min appeared to have similar pharmacokinetic profiles of all irinotecan, SN-38, and SN-38G to those with normal renal function (Ccr ≥ 60 mL/min). Our results also suggest that there is no difference in patient susceptibility to irinotecan-induced cholinergic syndrome (pharmacodynamics) based on renal function as measured by Ccr.

It has been reported that cigarette smokers showed a significantly lower dose-normalized area under the plasma concentration–time curve of irinotecan than nonsmokers by the potential induction of carboxylesterase enzyme, which catalyzes irinotecan conversion to SN-38, by cigarette smoke components [37]. Furthermore, smokers showed an almost 40% lower exposure to SN-38 as well as a higher relative extent of glucuronidation of SN-38 into SN-38G, probably owing to the upregulation of the UGT1A1 enzyme by cigarette smoke. Although smokers experienced considerably less hematologic toxicity in a previous study [37], our results demonstrated that smoking cigarettes was not correlated with irinotecan-induced cholinergic syndrome. The pharmacokinetic profiles of irinotecan and its metabolites in our smoking patient population may not be sufficiently altered to induce cholinergic syndrome.

Our study had several limitations. First, it was a retrospective observational study in which information on cholinergic syndrome was collected from medical records written by medical oncologists based on patient complains, without any predetermined criteria, which may lead to potential bias in both patient and their evaluation. The severities

of cholinergic syndrome symptoms were not investigated because of the lack of such information in medical records. Second, we did not investigate concomitant medications that may have affected the onset of irinotecan-induced cholinergic syndrome except for anticholinergics prescribed for the symptom by medical oncologists.

In conclusion, our study demonstrated for the first time that the addition of cytotoxic chemotherapeutic agent(s) coadministered with irinotecan is positively correlated with the onset of irinotecan-induced cholinergic syndrome.

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to declare in association with this study.

References

1. Fujita K, Kubota Y, Ishida H et al (2015) Irinotecan, a key chemotherapeutic drug for metastatic colorectal cancer. World J Gastroenterol 21(43):12234–12248. https://doi.org/10.3748/wjg.v21.i43.12234
2. Mathijssen RH, van Alphen RJ, Verweij J et al (2001) Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). Clin Cancer Res 7(8):2182–2194
3. Ando Y, Saka H, Ando M et al (2000) Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 60(24):6921–6926
4. Innocenti F, Undevia SD, Iyer L et al (2004) Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 22(8):1382–1388. https://doi.org/10.1200/JCO.2004.07.173
5. Araki K, Fujita K, Ando Y et al (2006) Pharmacogenetic impact of polymorphisms in the coding region of the *UGT1A1* gene on SN-38 glucuronidation in Japanese patients with cancer. Cancer Sci 97(11):1255–1259. https://doi.org/10.1111/j.1349-7006.2006.00321.x
6. Minami H, Sai K, Saeki M et al (2007) Irinotecan pharmacokinetics/pharmacodynamics and *UGT1A* genetic polymorphisms in Japanese: roles of *UGT1A1*6* and *28. Pharmacogenet Genom 17(7):497–504. https://doi.org/10.1097/FPC.0b013e328014341f
7. Gandia D, Abigerges D, Armand JP et al (1993) CPT-11-induced cholinergic effects in cancer patients. J Clin Oncol 11(1):196–197. https://doi.org/10.1200/JCO.1993.11.1.196
8. Miya T, Fujikawa R, Fukushima J et al (1998) Bradycardia induced by irinotecan: a case report. Jpn J Clin Oncol 28(11):709–711
9. Fujii H, Hirata T, Mura T et al (2018) Relation between irinotecan-induced cholinergic syndrome and prognosis of colorectal cancer patients. J Clin Oncol 36(4_suppl):859. https://doi.org/10.1200/JCO.2018.36.4_suppl.859
10. Kanbayashi Y, Ishikawa T, Kanazawa M et al (2018) Predictive factors for the development of irinotecan-related cholinergic syndrome using ordered logistic regression analysis. Med Oncol 35(6):82. https://doi.org/10.1007/s12032-018-1142-3
11. Pitot HC, Goldberg RM, Reid JM et al (2000) Phase I dose-finding and pharmacokinetic trial of irinotecan hydrochloride (CPT-11) using a once-every-three-week dosing schedule for patients with advanced solid tumor malignancy. Clin Cancer Res 6(6):2236–2244
12. Blandizzi C, De Paolis B, Colucci R et al (2001) Acetylcholinesterase blockade does not account for the adverse cardiovascular effects of the antitumor drug irinotecan: a preclinical study. Toxicol Appl Pharmacol 177(2):149–156. https://doi.org/10.1006/taap.2001.9293
13. Tsavaris N, Ziras N, Kosmas C et al (2003) Two different schedules of irinotecan (CPT-11) in patients with advanced colorectal carcinoma relapsing after a 5-fluorouracil and leucovorin combination. A randomized study. Cancer Chemother Pharmacol 52(6):514–519. https://doi.org/10.1007/s00280-003-0659-z
14. Schoemaker NE, Kuppens IE, Moiseyenko V et al (2004) A randomised phase II multicentre trial of irinotecan (CPT-11) using four different schedules in patients with metastatic colorectal cancer. Br J Cancer 91(8):1434–1441. https://doi.org/10.1038/sj.bjc.6602172
15. Tournigand C, André T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22(2):229–237. https://doi.org/10.1200/JCO.2004.05.113
16. Noda K, Nishiwaki Y, Kawahara M et al (2002) Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346(2):85–91. https://doi.org/10.1056/NEJMoa003034
17. Yoshida K, Iwashita T, Uemura S et al (2017) A multicenter prospective phase II study of first-line modified FOLFIRINOX for unresectable advanced pancreatic cancer. Oncotarget 8(67):111346–111355. https://doi.org/10.18632/oncotarget.22795
18. Sunakawa Y, Fujita K, Ichikawa W et al (2012) A phase I study of infusional 5-fluorouracil, leucovorin, oxaliplatin and irinotecan in Japanese patients with advanced colorectal cancer who harbor UGT1A1*1/*1,*1/*6 or *1/*28. Oncology 82(4):242–248. https://doi.org/10.1159/000337225
19. Cunningham D, Humblet Y, Siena S et al (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351(4):337–345. https://doi.org/10.1056/NEJMoa033025
20. Peeters M, Price TJ, Cervantes A et al (2010) Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 28(31):4706–4713. https://doi.org/10.1200/JCO.2009.27.6055
21. Yamazaki K, Nagase M, Tamagawa H et al (2016) Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). Ann Oncol 27(8):1539–1546. https://doi.org/10.1093/annonc/mdw206
22. Van Cutsem E, Tabernero J, Lakomy R et al (2012) Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 30(28):3499–3506. https://doi.org/10.1200/JCO.2012.42.8201
23. Tabernero J, Yoshino T, Cohn AL et al (2015) Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 16(5):499–508. https://doi.org/10.1016/S1470-2045(15)70127-0
24. Matsumoto K, Katsumata N, Yamanaka Y et al (2006) The safety and efficacy of the weekly dosing of irinotecan for platinum- and

taxanes-resistant epithelial ovarian cancer. Gynecol Oncol 100(2):412–416. https://doi.org/10.1016/j.ygyno.2005.10.013
25. Hironaka S, Ueda S, Yasui H et al (2013) Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 31(35):4438–4444. https://doi.org/10.1200/JCO.2012.48.5805
26. Shimada Y, Yoshino M, Wakui A et al (1993) Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. CPT-11 Gastrointestinal Cancer Study Group. J Clin Oncol 11(5):909–913. https://doi.org/10.1200/JCO.1993.11.5.909
27. Muro K, Boku N, Shimada Y et al (2010) Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol 11(9):853–860. https://doi.org/10.1016/S1470-2045(10)70181-9
28. Valencak J, Raderer M, Kornek GV et al (1998) Irinotecan-related cholinergic syndrome induced by coadministration of oxaliplatin. J Natl Cancer Inst 90(2):160
29. Cheng C, Lau JE, Earl MA (2015) Use of atropine-diphenoxylate compared with hyoscyamine to decrease rates of irinotecan-related cholinergic syndrome. J Commun Support Oncol 13(1):3–7. https://doi.org/10.12788/jcso.0099
30. Marsh ReW, Talamonti MS, Katz MH et al (2015) Pancreatic cancer and FOLFIRINOX: a new era and new questions. Cancer Med 4(6):853–863. https://doi.org/10.1002/cam4.433
31. Lambert A, Gavoille C, Conroy T (2017) Current status on the place of FOLFIRINOX in metastatic pancreatic cancer and future directions. Therap Adv Gastroenterol 10(8):631–645. https://doi.org/10.1177/1756283X17713879
32. Fujita K, Sasaki Y (2014) Optimization of cancer chemotherapy on the basis of pharmacokinetics and pharmacodynamics: from patients enrolled in clinical trials to those in the 'real world'. Drug Metab Pharmacokinet 29(1):20–28
33. Blandizzi C, Danesi R, De Paolis B et al (2002) Cholinergic toxic syndrome by the anticancer drug irinotecan: acetylcholinesterase does not play a major role. Clin Pharmacol Ther 71(4):263–271. https://doi.org/10.1067/mcp.2002.121909
34. Akiyama Y, Fujita K, Nagashima F et al (2008) Genetic testing for *UGT1A1*28* and **6* in Japanese patients who receive irinotecan chemotherapy. Ann Oncol 19(12):2089–2090. https://doi.org/10.1093/annonc/mdn645
35. Beutler E, Gelbart T, Demina A (1998) Racial variability in the UDP-glucuronosyltransferase 1 (*UGT1A1*) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci USA 95(14):8170–8174
36. de Jong FA, van der Bol JM, Mathijssen RH et al (2008) Renal function as a predictor of irinotecan-induced neutropenia. Clin Pharmacol Ther 84(2):254–262. https://doi.org/10.1038/sj.clpt.6100513
37. van der Bol JM, Mathijssen RH, Loos WJ et al (2007) Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. J Clin Oncol 25(19):2719–2726. https://doi.org/10.1200/JCO.2006.09.6115