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ORIGINAL ARTICLE

Irinotecan-induced neutropenia is reduced by oral alkalization drugs: analysis using retrospective chart reviews and the spontaneous reporting database

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Abstract

Purpose SN-38, an active metabolite of irinotecan, is reabsorbed by the intestinal tract during excretion, causing diarrhoea and neutropenia. In addition, the association between blood levels of SN-38 and neutropenia has been reported previously, and the rapid excretion of SN-38 from the intestinal tract is considered to prevent neutropenia. Oral alkalization drugs are used as prophylactic agents for suppressing SN-38 reabsorption. The relationship between oral alkalization drugs and neutropenia, however, has not been well studied. The aim of this study was to investigate the relationship between oral alkalization drugs and neutropenia in irinotecan-treated patients.

Methods and results Patients with cervical or ovarian cancer were administered irinotecan and investigated by medical chart reviews to determine whether oral alkalization drugs were effective at ameliorating irinotecan-induced neutropenia. The drug combination in the oral alkalization drugs—ursodeoxycholic acid, magnesium oxide, and sodium hydrogen carbonate—significantly improved neutrophil counts and reduced dose intensity compared with those of non-users. In the large-scale Japanese Adverse Drug Event Report database, the reporting odds ratio of irinotecan-induced neutropenia was significantly lower when irinotecan had been given in combination with oral alkalization drugs.

Conclusions These data indicate that oral alkalization drugs may reduce the frequency of neutropenia caused by irinotecan administration, making it possible to increase the dose safely.

Keywords Irinotecan · SN-38 · Alkalization drugs · JADER · Supportive care

Hirofumi Hamano and Marin Mitsui contributed equally to this work.

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Irinotecan hydrochloride is a prodrug of SN-38, which is a potent inhibitor of topoisomerase I [1]. Irinotecan is indicated for use as an anticancer drug for various cancer types. In particular, treatment is very useful for platinum-resistant recurrent cervical [2] and recurrent ovarian cancer [3]. However, treatment can be accompanied by adverse events including neutropenia and diarrhoea, which contribute to irinotecan's dose-limiting toxicities [4].

Irinotecan-induced diarrhoea can be prevented by several drugs [5–7], but there is no prophylactic drug for neutropenia. Irinotecan-induced neutropenia correlates with blood SN-38 levels [8]. The major mechanism of clearance of SN-38 is glucuronidation to SN-38 glucuronide (SN-38G) by *UGT1A1* [9], and a genetic polymorphism in *UGT1A1* increases the rate of incidence of severe neutropenia [10, 11]. In other words, an excretion delay of SN-38 increases the risk of neutropenia occurrence. In clinical practice, irinotecan-induced diarrhoea is prevented using oral alkalization drugs (OA) [7]. OA are composed of ursodeoxycholic acid, magnesium oxide, and sodium hydrogen carbonate and are administered to suppress reabsorption and promote the excretion of SN-38 from the intestinal tract. Therefore, OA could also reduce irinotecan-induced neutropenia, thereby reducing its dose-limiting toxicity. The relationship between OA and neutropenia has not yet been investigated thoroughly.

The Japanese Adverse Drug Event Report (JADER) is a large database of self-reported adverse drug events that reflects the realities of clinical practice. Recently, large databases have received attention as methods to discover new drug interactions [12–14]. The JADER has therefore been recognised as one of the primary tools for pharmacovigilance assessments in Japan. In this study, we aimed to evaluate the relationship between OA and neutropenia in irinotecan-administered patients. Our primary objective was to explore whether OA relieve irinotecan-induced neutropenia via a case–control study using hospital electronic medical charts. Our secondary objective was to explore the trends on a multicentre scale by using the JADER database.

Materials and methods

Study population

We retrospectively reviewed the medical charts of patients who were administered irinotecan for the treatment of recurrent cervical or recurrent ovarian cancer, which are sometimes treated with irinotecan monotherapy, from January 2007 to December 2016 at Tokushima University Hospital. In the irinotecan monotherapy regimen, irinotecan (100 mg/m^2) was used on day 1. Patients were excluded if they had hyperbilirubinemia (total bilirubin levels above 1.5 mg/dL) or received dialysis; accumulation of uremic toxin due to renal failure results in decreased organic anion transporter expression in the liver, which leads to delayed metabolism of irinotecan [15, 16]. Of the 55 patients eligible for this study, 18 were treated with OA, including ursodeoxycholic acid (0.3 g/day), magnesium oxide (dose of 2 g/day or less is regulated to prevent constipation) and sodium hydrogen carbonate (1.8 g/day), each on days 1–4 [7]; if patients had watery diarrhoea, magnesium oxide is stopped, and 37 did not receive OA as clinical practice.

Data collection of electronic medical charts

Data procured from the electronic medical charts included sex, age, anticancer treatment history, laboratory data, dose intensity (DI) of irinotecan, survival outcome, and adverse events after chemotherapy. For each adverse event, the severity was assessed using Common Terminology Criteria for Adverse Events v4.0. The DI was a measure of the protocol-directed or drug dose delivered per time unit; common units for DI are mg/m^2/week.

Definition of adverse events

We used the World Medical and Drug Information Service to define drug names (Supplementary Table 2). Disease names were defined using the Medical Dictionary for Regulatory Activities (MedDRA/J) version18 (Supplementary Table 3). The words used in the analysis were decided by consensus by our study team, which included a physician and a clinical pharmacist.

Large-scale database analysis

Adverse event data recorded in the JADER from January 2004 to January 2015 (among a total of 430,587 reports) were obtained from the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp) and consisted of four tables: patient demographics (DEMO), drug information and administration records (DRUG), adverse events (REAC) and primary disease (HIST). We excluded reports that were missing patient age range or sex. Ages are provided as a 10-year interval; patient data were therefore classified into two groups—younger than 60 years and older than 60 years. Our analyses were performed according to methods previously described [17]; the reports were divided into the following (a) to (d) groups for the reporting odds ratio (ROR) at 95% confidence interval (CI): (a) individuals who received irinotecan ± OA and exhibited neutropenia; (b) individuals who received irinotecan ± OA but did not exhibit neutropenia; (c) individuals who did not receive irinotecan ± OA and exhibited neutropenia and (d) individuals who did not receive irinotecan ± OA and did not exhibit neutropenia. ROR was calculated for groups (a) to (d) by the following equation:

$$\mathrm{ROR} = (a/b)/(c/d), 95\%\mathrm{CI}$$
$$= \exp\left[\log(\mathrm{ROR}) \pm 1.96\sqrt{(1/a + 1/b + 1/c + 1/d)}\right]$$

Statistical analysis of electronic medical charts

Case record data are shown as mean ± standard deviation (SD). Fisher's exact probability test, Pearson's chi-square test, Mann-Whitney *U* test and Student's *t* test were used to assess differences between the OA non-user group and the OA user group. The doses of irinotecan, neutrophil count at first cycle and dose adjustment of irinotecan at the next chemotherapy course were compared using unpaired Student's *t* tests. Adverse events after the first chemotherapy course were assessed via Fisher's exact probability test or Pearson's chi-square test. In addition, the Kaplan-Meier method was used for survival analysis, and the log-rank test was used to compare the two groups. All recorded *P* values were two-sided; *P* values <0.05 were considered statistically significant.

Statistical analysis of large-scale database

For the large-scale database analysis, we used ROR, a signal detection method, to evaluate the safety of the antitumour drug. When the calculated lower limit value of the 95% CI of ROR exceeded 1, it was assumed that there was a signal [17].

Results

Patient characteristics

A total of 55 patients, treated with irinotecan for cervical or ovarian cancer, were selected for inclusion in this study. Table 1 shows the characteristics of irinotecan-treated patients who were OA non-users ($n = 37$) and OA users ($n = 18$). The median patient age was 61.8 years (range = 35–82 years) for OA non-users and 64.3 years (range = 41–80 years) for OA users. All patients were women, and there were no significant differences between the two treatment groups with respect to the other parameters shown in Table 1.

OA alleviate irinotecan-induced neutropenia

We first investigated the effect of OA on irinotecan-induced neutropenia. The neutrophil count before irinotecan administration was 3791 ± 1420/μL in the OA non-user group and 3730 ± 1626/μL in the OA user group. In the first cycle of irinotecan treatment, the lowest neutrophil counts were 1591 ± 1149/μL in the OA non-user group and 2697 ± 1860/μL in the OA user group ($P = 0.009$) (Fig. 1a). When the neutrophil nadir was evaluated based on grade, the incidence of at least grade 2 neutropenia was 56.8% (21/37) in the OA non-user group and 27.8% (5/18) in the OA user group ($P = 0.043$). The proportion of patients who experienced grade 3/4 neutropenia was not significantly different between the OA non-user group (27.0%) and the OA user group (22.2%) ($P = 0.755$) (Fig. 1b).

OA limit necessity of irinotecan dose reduction

Next, we analysed the DI, of the average weekly dose of irinotecan. DI was significantly greater for OA users than for OA non-users (OA non-user 61.6 ± 27.4 mg/m^2/week vs. OA user 80.6 ± 21.8 mg/m^2/week, $P = 0.012$) (Fig. 2a). In addition, overall survival (OS) was compared between the two groups. The median OS was 9.0 weeks for the OA non-user group and 11.5 weeks ($P = 0.129$) for the OA user group (Fig. 2b). These findings suggest that co-administration of OA did not result in an irinotecan dose reduction and may maintain or prolong OS.

Influence of combination treatment with OA on the incidence of adverse events of irinotecan

There were no statistical differences between the two groups for other adverse events, such as anaemia, thrombocytopenia and acute kidney injury. Gastrointestinal symptoms such as anorexia and diarrhoea were alleviated after the combined treatment with OA, but the difference was not statistically significant (Table 2). We also checked transaminase and hyperbilirubinemia, but neither developed in the two groups (data not shown).

Irinotecan-induced neutropenia based on JADER database

Based on the data at Tokushima University Hospital, a larger analysis to evaluate the influence of OA in irinotecan-induced neutropenia using data from many hospitals was conducted using the JADER. Prior to analysis, we investigated the involvement of confounding variables in irinotecan-induced neutropenia-related adverse events (Supplementary Table 1). Specifically, we stratified by age, sex and primary disease. Treatment with irinotecan increased the incidence of neutropenia (ROR = 6.40, 95% CI = 6.05–6.77). Next, we stratified the affected individuals by age. The incidence of neutropenia increased after using irinotecan but did not differ greatly between patients younger than 60 years and those older than 60 years. Neutropenia increased in both men and women, but the ROR was higher in women. Finally, when stratifying based on primary disease for which irinotecan was indicated (colorectal, stomach, gynaecological and lung cancers), the incidence of neutropenia remained high. These results suggest

Table 1 Baseline clinicopathological characteristics of irinotecan-treated patients

Characteristic	OA non-users No. of patients (%)	OA users No. of patients (%)	*P* value
Total no.	37 (100.0)	18 (100.0)	
Age, years (mean, range)	61.8 (35–82)	64.3 (41–80)	0.47
< 60	12 (32.4)	7 (38.9)	0.64
≥ 60	25 (67.6)	11 (61.1)	
Sex			
Man	0 (0.0)	0 (0.0)	–
Woman	37 (100.0)	18 (100.0)	
ECOG performance status			
0/1	27 (73.0)	10 (55.6)	0.20
2/3/4	10 (27.0)	8 (44.4)	
Previous treatment lines			
Second line	3 (8.1)	2 (11.1)	1.00
Third line or more	34 (91.9)	16 (88.9)	

ECOG = Eastern Cooperative Oncology Group

that irinotecan was significantly associated with an increased occurrence of neutropenia, regardless of the indication for use.

OA treatment reduced irinotecan-induced neutropenia based on JADER database

We considered confounding variables and analysed the influence of OA on irinotecan-induced neutropenia in the JADER. We examined the ROR of irinotecan-induced neutropenia when using any one of the OA components (all alkalization drugs) or only one of the OA components (ursodeoxycholic acid, magnesium oxide, or sodium hydrogen carbonate) adjunctively (Table 3). The ROR for all alkalization drugs (ROR = 0.74, 95% CI = 0.62–0.88) was statistically significant. For the individual OA components, the ROR for magnesium oxide (ROR = 0.76, 95% CI = 0.63–0.91) was statistically significant, while those for ursodeoxycholic acid (ROR = 0.76, 95% CI = 0.54–1.06) and sodium hydrogen carbonate (ROR = 1.04, 95% CI = 0.72–1.52) were not significant.

Influence of combination treatment with OA on reducing neutropenia in certain patient groups based on JADER database

To examine the characteristics of patients who benefitted from the effect of OA in reducing irinotecan-induced neutropenia, we stratified by age or sex and calculated ROR (Table 4). With all alkalization drugs, the incidence in neutropenia in the under 60 years group was slightly lower than that in the older group (younger: ROR = 0.67, 95% CI = 0.47–0.95 vs. aged: ROR = 0.76, 95% CI = 0.62–0.93). When stratified by sex, the incidence of neutropenia was not significant for men but was statistically significant for women and was dependent on sex (men: ROR = 0.81,

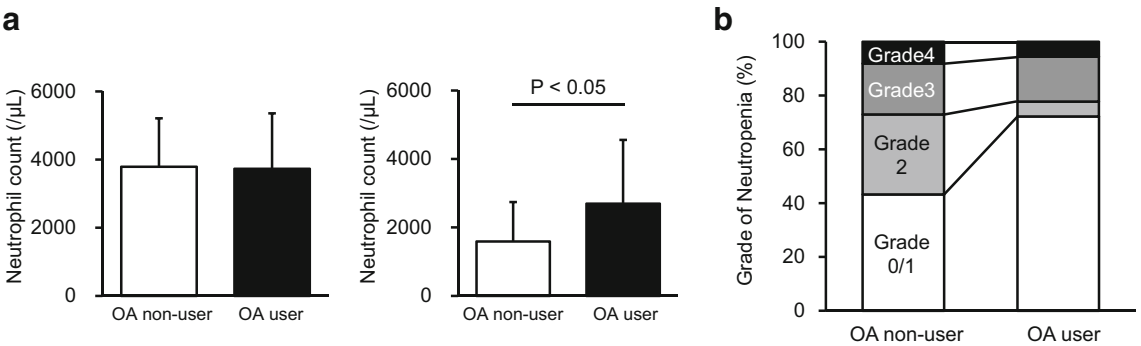
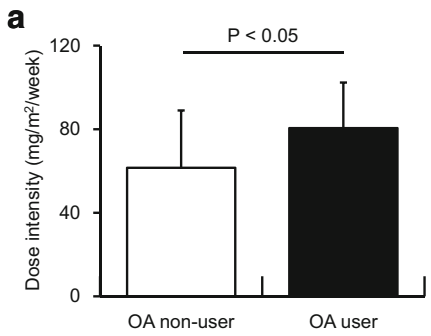


Fig. 1 OA effect on irinotecan-induced neutropenia onset. **a** Changes in neutrophil count from patients receiving irinotecan treatment with and without concomitant OA. Left panel; neutrophil count immediately before irinotecan treatment. Right panel; neutrophil count nadir in the first cycle of irinotecan treatment. Values are expressed as means ± SD. *n* = 18–37 per group. **b** Grade of neutropenia from patients receiving irinotecan without OA (OA non-user) or with OA (OA user) in the first cycle. *n* = 18–37 in each group. Abbreviations: OA oral alkalization drugs



Reason for chemotherapy stop	OA non-user	OA user
Neutropenia or febrile neutropenia	11	2
Thrombocytopenia	1	0
Anorexia	4	2
Diarrhoea	2	0
Ileus	1	0
Urinary tract obstruction	3	0

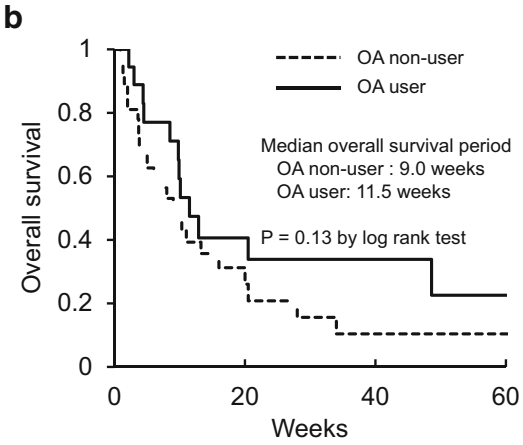


Fig. 2 OA impact on the effectiveness of irinotecan. **a** Differences in irinotecan dosage for treatment with and without OA. Upper bar graph; dose intensity for patients with and without OA treatment. Lower table; reason for irinotecan treatment withdrawal. Values are expressed as means ± SD. $n = 18$–37 in each group. **b** Overall survival of patients with irinotecan treatment with and without OA. $n = 18$–37 in each group

95% CI = 0.65–1.01 vs. women: ROR = 0.63, 95% CI = 0.48–0.83).

Discussion

Our study of electronic medical charts and the JADER suggests that OA can maintain the safety and efficacy of irinotecan treatment by reducing irinotecan-induced neutropenia.

There are limited medications currently available for the prevention of neutropenia. Pegfilgrastim [18], a long-acting granulocyte colony-stimulating factor analogue, is generally known. However, evidence for use of this medicine for irinotecan-induced neutropenia is lacking because the incidence rate of irinotecan-induced febrile neutropenia is lower than 20% [19]. A previous study on OA [7] suggested that OA are effective in preventing delayed diarrhoea in cisplatin/irinotecan combination therapy. This report also suggested that OA are protective of leukocyte levels, but there was no significant difference in the number of granulocytes at the nadir, which may be due to the bias of cisplatin toxicity. Our study is supported by the analysis of irinotecan use alone, as well as a large spontaneous reporting database; these analyses can further reduce the potentially confounding factors of other anticancer drugs and single-centre bias. Our finding that treatment with OA was significantly protective in maintaining neutrophil levels therefore support the previous OA study and presents strong evidence regarding the efficacy of OA as a preventive treatment against irinotecan-induced neutropenia.

OA are composed of ursodeoxycholic acid, magnesium oxide, and sodium hydrogen carbonate; they are concomitantly used with irinotecan to suppress the increase in molecular type SN-38 in the intestinal tract. These three medicines alkalise the intestinal tract and the biliary tract [20]; magnesium oxide also prevents constipation and shortens the SN-38 exposure time. The lactone ring of the SN-38 structure undergoes reversible opening and closing due to pH changes

Table 2 Adverse events in irinotecan-treated OA non-users ($n = 37$) and OA users ($n = 18$)

Adverse event	All grades (no. of patients, %)		P value	Grade 3/4 (no. of patients, %)		*P* value
	OA non-users	OA users		OA non-users	OA users	
Anaemia	28 (75.7)	9 (50.0)	0.06	18 (48.6)	7 (38.9)	0.50
Thrombocytopenia	2 (5.4)	0 (0.0)	1.00	1 (2.7)	0 (0.0)	1.00
Anorexia	21 (56.8)	6 (33.3)	0.10	7 (18.9)	1 (5.6)	0.19
Diarrhoea	16 (43.2)	5 (27.8)	0.38	7 (18.9)	2 (11.1)	0.70
Acute kidney injury	3 (8.1)	1 (5.6)	1.00	0 (0.0)	0 (0.0)	1.00

Table 3 Effect of OA treatment in reducing irinotecan-induced neutropenia in JADER

OA component used in combination with irinotecan	Neutropenia without OA component (%)	Neutropenia with OA component (%)	Odds ratio (95% CI)	*P* value
Ursodeoxycholic acid	1732/6096 (28.4%)	45/195 (23.1%)	0.76 (0.54–1.06)	0.11
Magnesium oxide	1613/5592 (28.8%)	164/699 (23.5%)	0.76 (0.63–0.91)	0.00
Sodium hydrogen carbonate	1738/6157 (28.2%)	39/134 (29.1%)	1.04 (0.72–1.52)	0.85
All alkalization drugs	1587/5471 (29.0%)	190/820 (23.2%)	0.74 (0.62–0.88)	0.00

[21]; under acidic conditions, it forms an anionic closed ring structure, and under alkaline conditions, it forms ionic open ring structures. CPT-11, SN-38 and SN-38G in bile are mostly ionic because bile is weakly alkaline. The intestinal environment is acidic (approximately pH 6.0) [22], thereby increasing the anionic form, which increases toxicity. Additionally, the anionic form promotes greater passive transport in small intestinal cells compared with that of the ionic form [21]; haematotoxicity also increases by promoting enterohepatic circulation. Conversely, increasing the pH to an alkaline condition allows intestinal reabsorption and haematotoxicity to be reduced [21]. In other words, alkalization by OA increases the SN-38 ionic type in the intestinal environment and inhibits enterohepatic circulation.

We confirmed the suppression of severe irinotecan-induced neutropenia by treatment with OA. By contrast, declining enterohepatic irinotecan circulation reduces the time irinotecan activator stays in the blood, which leads

Table 4 Stratification of OA effects in irinotecan-induced neutropenia in JADER

Younger				
OA component used in combination with irinotecan	Reports (153742)	Neutropenia (8669)		
	No. of OA component users	No. of neutropenia cases (%)	Odds ratio (95% CI)	*P* value
Ursodeoxycholic acid	55	10 (18.2%)	0.59 (0.29–1.17)	0.16
Magnesium oxide	158	34 (21.5%)	0.71 (0.48–1.06)	0.11
Sodium hydrogen carbonate	36	7 (19.4%)	0.64 (0.28–1.47)	0.35
All alkalization drugs	208	43 (20.7%)	0.67 (0.47–0.95)	0.02
Aged				
OA component used in combination with irinotecan	Reports (242494)	Neutropenia (15709)		
	No. of OA component users	No. of neutropenia cases (%)	Odds ratio (95% CI)	*P* value
Ursodeoxycholic acid	140	35 (25.0%)	0.83 (0.56–1.22)	0.39
Magnesium oxide	541	130 (24.0%)	0.76 (0.62–0.94)	0.01
Sodium hydrogen carbonate	98	32 (32.7%)	1.21 (0.79–1.86)	0.37
All alkalization drugs	612	147 (24.0%)	0.76 (0.62–0.93)	0.00
Man				
OA component used in combination with irinotecan	Reports (201922)	Neutropenia (12318)		
	No. of OA component users	No. of neutropenia cases (%)	Odds ratio (95% CI)	*P* value
Ursodeoxycholic acid	126	30 (23.8%)	0.86 (0.57–1.31)	0.54
Magnesium oxide	419	99 (23.6%)	0.84 (0.67–1.07)	0.18
Sodium hydrogen carbonate	81	24 (29.6%)	1.17 (0.72–1.90)	0.53
All alkalization drugs	500	115 (23.0%)	0.81 (0.65–1.01)	0.07
Woman				
OA component used in combination with irinotecan	Reports (194314)	Neutropenia (12060)		
	No. of OA component users	No. of neutropenia cases (%)	Odds ratio (95% CI)	*P* value
Ursodeoxycholic acid	69	15 (21.8%)	0.60 (0.34–1.07)	0.09
Magnesium oxide	280	65 (23.2%)	0.63 (0.47–0.84)	0.00
Sodium hydrogen carbonate	53	15 (28.3%)	0.86 (0.47–1.58)	0.76
All alkalization drugs	320	75 (23.4%)	0.63 (0.48–0.83)	0.00

to a decrease in irinotecan blood concentration. The antitumour effect of SN-38 acts specifically at the S phase (DNA synthesis phase) of the cell cycle and shows a time-dependent antitumour effect [1]. Accordingly, a reduction in the blood residence time of irinotecan may attenuate its antitumour effect; however, other temporary interruptions and postponements of treatment due to adverse events are also factors that influence the antitumour effect. In our study, the most common reasons for interruption and postponement of irinotecan treatment were neutropenia and febrile neutropenia. Therefore, the administration of irinotecan in combination with OA greatly reduced the incidence of therapy interruptions (Fig. 2a). Due to the reduced risk of discontinuation of treatment by the onset of neutropenia, the dose per unit time of irinotecan increased, and, as a result, OS was extended (Fig. 2a, b).

Our single-centre findings were supported by the results of the large-scale database analysis. The ROR of irinotecan-induced neutropenia was reduced after treatment with OA; surprisingly, other drugs that prevent delayed diarrhoea did not have the same effect (data not shown). Hangeshashinto did not affect the risk of neutropenia, and loperamide increased the risk of neutropenia. The Chinese medicine hangeshashinto contains ougon, which inhibits β-glucuronidase activity, preventing hydrolysis of SN-38G to SN-38 by enteric bacteria [23]. Hangeshasinto probably does not inhibit intestinal reabsorption, because SN-38G cannot be transferred to the open ring form. Loperamide slows the rhythm of the intestinal tract, allowing increased reabsorption of SN-38. When sorting by age or sex, patients younger than 60 years of age were better suited for concomitant OA treatment, with a lower ROR compared to that in patients older than 60 years of age. Ageing raises the pH in the body and can aid in the excretion of irinotecan; this may reduce the effect of OA in decreasing pH [24, 25]. The therapeutic benefit was greater for women; a greater reduction in the ROR for irinotecan-induced neutropenia was achieved with concomitant treatment of OA in women than in men. Hormones may play a role in this difference. Women have more gastrointestinal problems than men. For example, oestrogen is thought to be involved in constipation [26]. Constipation caused by oestrogen not only deteriorates the enterohepatic circulation but also increases intestinal bacteria, which acidify the intestinal environment. Indeed, women are more likely to reabsorb irinotecan because of the higher odds ratio of irinotecan-induced neutropenia compared with that of men. In the past, many studies on the metabolism of irinotecan, such as *UGT1A1* mutation studies, have been performed, but there is little information regarding its relationship with excretion. In this study, we suggest that by adjusting not only metabolism but also excretion, it is possible to reduce the variation in frequency of adverse events caused by irinotecan treatment among patients, making it possible to safely increase the treatment intensity. Therefore, OA may be most beneficial for patients who are older and women who have difficulties excreting irinotecan.

The major limitation of our study is that we were unable to determine all mutations in *UGT1A1* (Supplementary Table 4), which may bias test results. The mutant gene allele of *UGT1A1* is found in approximately 10% of Japanese individuals and strongly contributes to neutropenia by increasing its in vivo toxicity due to decreased glucuronidation [11]. In any event, there was no difference in *UGT1A1* mutations between the OA non-user group and OA user group. We were likewise unable to confirm compliance with OA use. There are factors that lead to reduced compliance, such as patients needing to take three drugs in combination; moreover, the powdered form of sodium hydrogen carbonate, can be difficult to take orally. A decrease in compliance, however, would lead to a reduction in the OA treatment effect for the adverse events of irinotecan and therefore is unlikely to greatly affect the test results. These study limitations are intrinsic to a retrospective study; therefore, we plan to explore these issues in a future prospective study.

In conclusion, we found that OA significantly reduced the frequency of neutropenia caused by irinotecan administration. Supplementation of irinotecan treatment with OA may enable increases in the safe dosage of irinotecan.

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Author contributions Study conception and design: H.H. Performed the experiments and data acquisition: H.H., M.M. Analysis and interpretation of data: H.H., M.M., Y.Z., K.T., T.N, N.O., K.F., Y.I., Y.H., Y.I., M.I., K.T., T.N., Y.K., H.F., H.Y., T.T. and K.I. Drafting the work or critically revising it for important intellectual content: H.H., Y.Z.

Compliance with ethical standards

This study and all protocols were reviewed and approved by the Ethics Committee of Tokushima University Hospital (approval number: 2059-4).

Conflict of interest The authors declare that they have no conflict of interest.

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