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Jansman, Frank G A; Idzinga, Froukje S F; Smit, Willem M; de Graaf, Jacques C; Coenen, Jules L L M; Sleijfer, Dirk Th; Brouwers, Jacobus R B J

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Brief Report

Classification and Occurrence of Clinically Significant Drug Interactions with Irinotecan and Oxaliplatin in Patients with Metastatic Colorectal Cancer

Frank G.A. Jansman, PharmD,[1,2] Froukje S.F. Idzinga, MSci,[1,2] Willem M. Smit, MD, PhD,[3] Jacques C. de Graaf, MD, PhD,[4] Jules L.L.M. Coenen, MD,[4] Dirk Th. Sleijfer, MD, PhD,[5] and Jacobus R.B.J. Brouwers, PharmD, PhD[2]

[1]*Department of Clinical Pharmacy, Isala Klinieken, Zwolle, the Netherlands;* [2]*Groningen University Institute for Drug Exploration, Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen, the Netherlands;* [3]*Department of Medical Oncology, Medisch Spectrum Twente, Enschede, the Netherlands;* [4]*Department of Medical Oncology, Isala Klinieken, Zwolle, the Netherlands; and* [5]*Department of Medical Oncology, University Hospital Groningen, Groningen, the Netherlands*

ABSTRACT

Background: Pharmacokinetic and pharmacodynamic drug interactions with cytotoxic drugs may significantly influence the efficacy and toxicity of chemotherapy.

Objective: The purpose of this study was to identify drug interactions with irinotecan and oxaliplatin reported in the literature, to assess their clinical significance, and to examine the occurrence of these interactions in patients with metastatic colorectal cancer treated with either irinotecan or oxaliplatin or both.

Methods: To obtain data on drug–drug interactions with irinotecan and oxaliplatin, a literature search of PubMed and EMBASE was conducted using the search terms *irinotecan*, *oxaliplatin*, and *interactions* (English-language studies only published between 1980 and August 2004). The interactions found were subsequently classified for documentation evidence and severity of clinical effect, according to a 5-level classification system of a standard reference text, by a study panel of medical oncologists and clinical pharmacists. Comedication of patients who were treated with irinotecan or oxaliplatin, or both, was then examined to determine the occurrence of clinically significant interactions.

Results: Ninety-eight patients (50 women, 48 men; mean age, 60 years) were included in the study. Seventeen interactions with irinotecan were found in the literature, and 11 were classified as clinically significant. Only 1 nonspecific, clinically significant interaction was identified for oxaliplatin. Irinotecan-treated patients received a mean of 8 different comedications and oxaliplatin-treated patients received a mean of 6. Apart from antiemetic and antidiarrheal drugs that were prescribed for treatment-related toxicities, only 1 patient appeared to be exposed to a possible clinically significant interaction (between irinotecan and phenytoin).

Conclusions: Eleven of the 17 interactions with irinotecan that were found in the literature were classified as clinically significant versus 1 clinically significant interaction with oxaliplatin. The occurrence of these interactions in the study patients with metastatic colorectal cancer was low. For medication surveillance purposes, however, the significant interactions should be considered in clinical practice. (*Clin Ther.* 2005;27:327–335) Copyright © 2005 Excerpta Medica, Inc.

Key words: colorectal neoplasms, chemotherapy, drug interactions, adverse effects, irinotecan, oxaliplatin, epidemiology.

INTRODUCTION

Drug interactions may significantly influence the efficacy and toxicity of cytotoxic treatment as a result of

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changes in pharmacokinetic and pharmacodynamic behavior of the cytotoxic drug involved. Because parenteral cytotoxic drugs are usually administered in a hospital setting, and most comedication is delivered by the community pharmacy department, incomplete medication surveillance may occur. Therefore, particular attention in terms of interactions with cytotoxic drugs is warranted.

Recently, results were presented from a study of the clinical significance of drug interactions with 5-fluorouracil (5-FU) in patients with colorectal cancer.[1] 5-FU has remained the mainstay of treatment for >4 decades for patients with colorectal cancer.[2,3] However, in the last 10 years, several new cytotoxic drugs—irinotecan, oxaliplatin, capecitabine, and tegafur in combination with uracil (UFT)—with activity as single agents have widened the spectrum of therapeutic options in colorectal cancer. Capecitabine and UFT are oral analogues of 5-FU and therefore can be assumed to have an interaction profile similar to 5-FU (ie, they will interact with the same agents that interact with 5-FU). Among the new parenteral drugs, irinotecan and oxaliplatin are increasingly being considered as first-line treatment for patients with metastatic colorectal cancer.[2,3] Data from 7 Phase III trials revealed that the use of combination treatments using 5-FU plus leucovorin, with either irinotecan or oxaliplatin, versus 5-FU alone significantly improved the median survival by 3.5 months ($P = 0.008$).[2] Therefore, in the present study, the potential pharmacokinetic and pharmacodynamic drug interactions with either agent were investigated. The purpose of this study was to identify drug interactions with irinotecan and oxaliplatin reported in the literature, to assess their clinical significance, and to examine the occurrence of these interactions in patients with metastatic colorectal cancer treated with either irinotecan or oxaliplatin or both.

PATIENTS AND METHODS

Patients and Comedication

Patients from 3 hospitals in Zwolle, Enschede, and Leeuwarden, the Netherlands, who were treated with irinotecan or oxaliplatin for metastatic colorectal cancer participated in the study. The study protocol was reviewed and approved by the Medical Ethical Committee of the hospitals in accordance with the International Conference on Harmonisation of Guidelines for Good Clinical Practice. The inclusion criteria matched the registered indications of both cytotoxic agents.[4,5] From January 2000 until April 2004, irinotecan-treated patients and oxaliplatin-treated patients were included after providing written informed consent.

Medication files were acquired from the community pharmacy and hospital pharmacy. In addition, patients were instructed to list their comedication, including nonprescription medications, homeopathic agents, food supplements, and herbal remedies. After collecting all data, comedication was classified according to the Anatomical Therapeutic Chemical (ATC) system, a hierarchic classification based on target organ or receptor, therapeutic effect, and chemical group, respectively.[6]

Drug Interactions

For quantification of the clinical significance of drug interactions, the classification scheme of the standard reference *Drug Interaction Facts*[7] was used. The interactions selected from the literature were examined based on the documentation evidence for the interaction and on the severity of the clinical effect of the interaction (**Table I**). The classification scheme according to *Drug Interaction Facts* distinguishes 5 levels of documentation based on the amount and quality of evidence available: established, probable, suspected, possible, and unlikely, in addition to 3 levels (ie, major, moderate, minor) of the severity of the interaction's clinical effect. As a result, 15 different categories for classification of potential drug–drug interactions emerge. These categories vary from unlikely based on the literature with an effect of minor severity, to established in the literature with an effect of major severity. For clinical significance, 5 levels were assigned to the 15 categories, with level 1 referring to an interaction that needs to be avoided in clinical practice by not using the combination and level 5 indicating no interaction to be determined.

To obtain data on drug–drug interactions with irinotecan and oxaliplatin, a literature search was performed using reference books, handbooks, and the electronic databases PubMed and EMBASE Drugs & Pharmacology. The MESH terms *irinotecan*, *oxaliplatin*, and *interactions* were used to search the PubMed and EMBASE databases for English-language studies published between 1980 and August 2004. All literature (full-length articles) regarding the interactions found was presented to a panel of medical oncologists and clinical pharmacists from the partici-

Table I. Clinical significance of drug interaction ratings according to the *Drug Interaction Facts* classification scheme.[7]

Severity of the Clinical Effect of the Interaction	Documentation Evidence				
	Established	Probable	Suspected	Possible	Unlikely
Major	1	1	1	4	5
Moderate	2	2	2	4	5
Minor	3	3	3	5	5

1 = avoid combination; 2 = usually avoid combination; 3 = minimize risk; 4 = no action needed; 5 = no interaction.

pating hospitals for classification of the interactions according to the guidelines shown in Table I. The agreement of the classification results between panel members was subsequently tested by calculating the weighted kappa (κ) coefficients.[8] Finally, the occurrence of the indicated clinically significant interactions was assessed in the study patients.

RESULTS

Patients and Comedication

In total, 98 patients (50 women, 48 men) were included, of whom 75 patients were treated with irinotecan and 52 patients were treated with oxaliplatin. Thus, 29 patients were treated with both irinotecan and oxaliplatin (administered in different cycles). The mean age of the patients was 60 years (range, 23–77 years).

Patients were treated according to different protocols.[4,5] Irinotecan was administered as follows: (1) as a single agent, 350 mg/m^2 by 30- to 90-minute continuous infusion, every 3 weeks, in 52 patients; (2) in combination with 5-FU/leucovorin, 180 mg/m^2 intravenously, every 2 weeks, in 2 patients, or 125 mg/m^2 intravenously, every week for 4 weeks in a 6-week cycle, in 6 patients; (3) in combination with capecitabine, 250 mg/m^2 intravenously, every 3 weeks, in 12 patients; and (4) in other combinations, using patient-specific dosing regimens, in 3 patients.

Oxaliplatin was given: (1) in combination with 5-FU/leucovorin, 85 mg/m^2 by 2- to 6-hour continuous infusion, every 2 weeks, in 50 patients; and (2) in combination with capecitabine, 130 mg/m^2 intravenously, every 3 weeks, in 2 patients. Treatment was continued until progression of the disease was detected.

For the 75 irinotecan-treated patients, 599 agents were prescribed as comedication, of which 545 were drugs. The other agents were predominantly homeopathic agents, herbal remedies, and food supplements. Among the agents listed as comedication, 161 different drugs and 47 different homeopathic agents, herbal remedies, and food supplements could be distinguished. Per patients, a mean of 8 agents (range, 0–30) was prescribed.

The results were similar for oxaliplatin-treated patients: 52 patients received prescriptions for 304 agents, of which 292 were drugs. Considering all comedication, 111 different drugs and 9 different homeopathic agents, herbal remedies, and food supplements were discerned. Per patient, a mean of 6 agents (range, 0–19) was prescribed.

The drugs that were prescribed as comedication during irinotecan and oxaliplatin treatment are shown in the figure, categorized according to the ATC classification. The figure shows that most drugs were from group A (alimentary tract and metabolism) and group N (nervous system). Drugs from the latter group were predominantly benzodiazepines and analgesics. The group of drugs classified as "Other" included mainly homeopathic and anthroposophic agents, multivitamins, and minerals. The 2 drugs most frequently reported as comedication in the irinotecan-treated group were metoclopramide and loperamide (both ATC group A drugs). In the oxaliplatin-treated group, the 2 drugs most often reported as comedication were metoclopramide and tropisetron (both ATC group A drugs).

Drug Interactions

The literature search for interactions with irinotecan and oxaliplatin resulted in a number of citations.[4,5,7,9–41] These publications were used by the panel of medical oncologists and clinical phar-

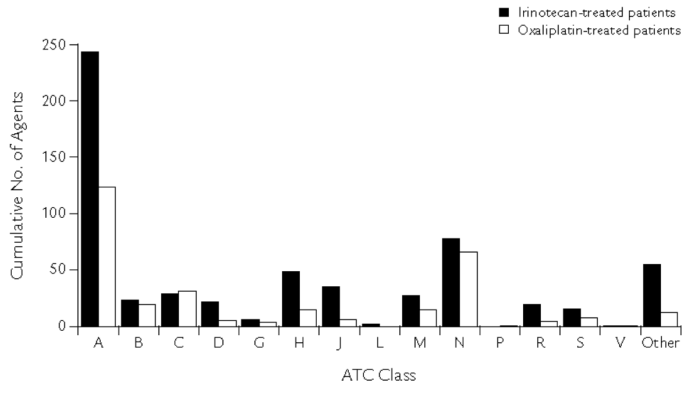

Figure. Comedication according to the Anatomical Therapeutic Chemical (ATC)[6] classification system during treatment with irinotecan and oxaliplatin in patients with metastatic colorectal cancer. ATC classification is as follows: A = alimentary tract and metabolism; B = blood and blood-forming organs; C = cardiovascular system; D = dermatologicals; G = genitourinary system and sex hormones; H = systemic hormonal preparations, excluding sex hormones and insulins; J = anti-infectives for systemic use; L = antineoplastic and immunomodulating agents; M = musculoskeletal system; N = nervous system; P = antiparasitic products, insecticides, and repellents; R = respiratory system; S = sensory organs; V = various.

macists to identify and classify the interactions. **Table II** lists the 17 drug interactions with irinotecan and 1 with oxaliplatin identified by the study panel.

The panel scored 12 interactions as clinically significant (ie, clinical significance level <4 in the classification system of *Drug Interaction Facts*[7]). The weighted κ coefficients for agreement of scores between panel members are presented in **Table III**. The κ coefficients varied from 0.41 to 0.95, indicating moderate to good classification agreement; there was a mean κ coefficient of 0.66, corresponding to substantial classification agreement.[8] Subsequent examination of the comedication that was prescribed for the irinotecan-treated patients revealed that for 71 patients at least 1 drug was identified that may have interacted significantly. The drugs involved were loperamide (64 patients [85% of the 75 patients who received irinotecan]), dexamethasone (45 patients [60%]), and phenytoin (1 patient [1%]). For oxaliplatin-treated patients, no potential significant drug interaction with comedication was found.

DISCUSSION

For the patients with metastatic colorectal cancer treated in this study with different dosing regimens of irinotecan or oxaliplatin, a mean of 8 or 6 agents, respectively, was reported as comedication. These amounts are similar to data from the literature regarding comedication in cancer patients.[1,20,21] Also, the mean age of 60 years in the present patient group is representative of colorectal cancer patients.[42] Most comedication agents were drugs from ATC group A (alimentary tract and metabolism)—that is, antiemetic and antidiarrheal agents—and from ATC group N (nervous system)—that is, benzodiazepines and analgesics. This is not surprising, since these drugs are used for prevention and management of adverse effects of chemotherapy, and for treatment of cancer-related pain.[43] Most frequently prescribed were the antiemetics metoclopramide and tropisetron, and the antidiarrheal drug loperamide.

Seventeen drug interactions with irinotecan were identified in the literature, of which 11 were classified as clinically significant. About half of the drug interactions were related to the hepatic drug metabo-

Table II. Interactions between irinotecan and oxaliplatin and noncytotoxic agents, as described in the literature. Clinically significant interactions (ie, level <4), according to the study panel, are given in italics (classified according to ratings of *Drug Interaction Facts*[7]).

	Clinical Significance Level*	Summary of Interaction	References
Agent interacting with irinotecan			
Aprepitant	4	Inhibition of CYP3A4 may result in elevated plasma concentrations of irinotecan.	Emend [product information][23]
Atazanavir	4	Irinotecan is metabolized by UGT1A1. Atazanavir inhibits this enzyme system. The combination may result in increased plasma concentrations of irinotecan and irinotecan toxicities.	Reyataz [product information][24]
Cyclosporine	2	*Cyclosporine inhibits the biliary excretion of irinotecan and its metabolites. In rats, pretreatment with cyclosporine resulted in an average increase of 339% and 361% in the AUC of irinotecan and SN-38, respectively.*	Herben et al[25] Gupta et al[26]
Citalopram	2	*Rhabdomyolysis occurred in a patient after concomitant use of irinotecan and citalopram. The rhabdomyolysis was exacerbated on reinitiation of citalopram and disappeared when the agent was discontinued.*	Richards et al[27]
Dexamethasone	3	*Concurrent use of dexamethasone and irinotecan may increase the risk of hyperglycemia in patients with diabetes mellitus or glucose intolerance. Combined use of irinotecan and dexamethasone as antiemetic prophylaxis may increase the risk of lymphocytopenia. In patients with malignant gliomas who received anticonvulsants or dexamethasone concomitantly with irinotecan, the AUC of irinotecan and its metabolites SN-38 and SN-38G were ~40%, 25%, and 25%, respectively, of those determined in colorectal cancer patients not receiving such comedication.*	Irinotecan [Drugdex drug evaluations][9] Friedman et al[28]
Folinic acid/leucovorin (calcium salts or sodium salts)	4	The C_{max} and AUC of SN-38 were reduced by 14% and 8%, respectively, when irinotecan was followed by fluorouracil and calcium folinate.	Irinotecan [Drugdex drug evaluations][9]
Ketoconazole	1	*Simultaneous administration of irinotecan, a CYP3A4 substrate, and ketoconazole, a CYP3A4 inhibitor, may result in increased formation of SN-38, an active metabolite of irinotecan. In 7 patients, the relative exposure to SN-38 was increased by 109%. Irinotecan is metabolized to APC by oxidation of its distal piperidine ring. This reaction was found to be inhibited by ketoconazole. In human cell lines, production of the oxidative metabolites APC, NPC, M2, and M4 from irinotecan was prevented by ketoconazole.*	Kehrer et al[29] Haaz et al[30] Santos et al[31]

(continued)

Table II. (Continued)

	Clinical Significance Level*	Summary of Interaction	References
Live vaccines/ rotavirus vaccine	3	*Vaccination with a live vaccine in a patient immuno-compromised by a chemotherapeutic agent has resulted in severe and fatal infections.*	General recommendations on immunizations[32]
Loperamide	3	*In human liver microsomes, loperamide significantly ($P < 0.001$) inhibited the oxidation of irinotecan to APC, and was found to inhibit the biotransformation of irinotecan to SN-38 in vitro.*	Herben et al[25] Haaz et al[30] Rivory et al[33]
Neomycin†	2	*The intestinal microflora appears capable of causing mucosal damage by metabolizing SN-38G to SN-38 and thus, irinotecan-induced gastrointestinal toxicity (eg, diarrhea). Simultaneous use of the antibiotics neomycin and bacitracin and irinotecan + 5-fluorouracil/leucovorin chemotherapy resulted in a decrease in both incidence and severity of irinotecan-induced diarrhea. Another study revealed that 5 out of 7 patients experienced no irinotecan-induced diarrhea during treatment with neomycin, whereas they had suffered from irinotecan-induced diarrhea before.*	Alimonti et al[34,35] Kehrer et al[36]
Neuromuscular blocking agents	4	Anticholinergic activity of irinotecan may prolong the neuromuscular block by suxamethonium and may antagonize the neuromuscular blocking by nondepolarizing agents.	Campto [product information][4]
Phenobarbital	2	*In rats, pretreatment with phenobarbital, an inducer of glucuronidation, caused a 1.7-fold increase in the AUC of SN-38G and a concomitant decrease in the AUCs of both SN-38 and irinotecan.*	Herben et al[25] Gupta et al[37]
Phenytoin	2	*The systemic exposure to irinotecan and SN-38 were reduced 79% and 92%, respectively, relative to data in the literature, by concomitant phenytoin therapy.*	Mathijssen et al[38]
St. John's wort	2	*St. John's wort reduced the AUC of SN-38 by 42%. Consequently, the degree of myelosuppression was substantially worse in the absence of St. John's wort.*	Mathijssen et al[39]
Thalidomide	1	*In an interim analysis of 9 patients, thalidomide had almost eliminated the dose-limiting gastrointestinal toxic effects of irinotecan.*	Govindarajan et al[40]
TJ-14 (Hange-Shashinto)	4	The Chinese herb TJ-14 (Hange-Shashinto) inhibits bacterial beta-glucuronidase activity in the intestine. Based on the results of a study with 19 evaluable patients, TJ-14 may prevent irinotecan-induced diarrhea.	Alimonti et al[35] Sakata et al[41]

(continued)

Table II. (Continued)

	Clinical Significance Level*	Summary of Interaction	References
Valproic acid	4	Coadministration of irinotecan with valproic acid, an inhibitor of glucuronidation, caused a 99% inhibition in the formation of SN-38G, leading to a 270% increase in the AUC of SN-38 compared with control rats; irinotecan AUC was unaltered.	Herben et al[25] Gupta et al[37]
Agent interacting with oxaliplatin			
Live vaccines/ rotavirus vaccine	3	*Vaccination with a live vaccine in a patient immunocompromised by a chemotherapeutic agent has resulted in severe and fatal infections.*	General recommendations on immunization[32]

CYP = cytochrome P-450; UGT1A1 = uridine 5′-diphosphate glucuronosyltransferase; SN-38 = 7-ethyl-10-hydroxycamptothecin; SN-38G = SN-38 glucuronide; APC = 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin; NPC = 7-ethyl-10-[4-(1-piperidino)-1-amino] carbonyloxycamptothecin.
*According to classification by the study panel of 3 medical oncologists and 3 clinical pharmacists.
†Potentially advantageous interaction.

Table III. Weighted kappa (κ) coefficients* for agreement between panel members of classification of interactions with irinotecan and oxaliplatin.

Panel Member†	1	2	3	4	5	6	Mean
1		0.43	0.47	0.57	0.41	0.48	0.47
2	0.43		0.81	0.59	0.71	0.82	0.67
3	0.47	0.81		0.64	0.90	0.95	0.75
4	0.57	0.59	0.64		0.68	0.71	0.64
5	0.41	0.71	0.90	0.68		0.80	0.70
6	0.48	0.82	0.95	0.71	0.80		0.75
Mean	0.47	0.67	0.75	0.64	0.70	0.75	0.66

*Judgment for agreement (according to Landis and Koch[8]): $\kappa \leq 0.20$, poor; $0.21 \leq \kappa \leq 0.40$, fair; $0.41 \leq \kappa \leq 0.60$, moderate; $0.61 \leq \kappa \leq 0.80$, substantial; $\kappa > 0.81$, good.
†Panel members 1 to 3 are medical oncologists, and 4 to 6 are clinical pharmacists.

lism of irinotecan, specifically the enzymes uridine 5′-diphosphate glucuronosyltransferase, cytochrome P-450 3A4, and carboxylesterase. Because oxaliplatin undergoes a series of spontaneous, nonenzymatic conversions in biological fluids, and oxaliplatin is not a substrate for cytochrome P-450,[5] no pharmacokinetic metabolic interactions were found in the literature. Moreover, except for a nonspecific interaction with vaccines that occurs with all cytostatic agents, no pharmacodynamic interactions with oxaliplatin have been reported.[44] This lack of published interactions may be due to the complex pharmacokinetic and pharmacodynamic properties of oxaliplatin, leaving possible interactions thus far indiscernible.

We recommend that the clinically significant interactions with irinotecan, as assessed by the study panel of medical oncologists and clinical pharmacists, be included in electronic databases for medication surveillance. In the present study, potential significant interactions with irinotecan were registered in 64 patients using loperamide, in 45 patients using dexa-

methasone, and in 1 patient using phenytoin. Dexamethasone and loperamide probably were given deliberately for the treatment of nausea and diarrhea, respectively. Because loperamide is mainly prescribed for the treatment of late diarrhea (ie, >24 hours after irinotecan administration, when irinotecan and 7-ethyl-10-hydroxycamptothecin [SN-38] are largely eliminated),[4,43] the clinical impact of the interaction is limited to patients that are treated earlier with this agent. However, phenytoin—which caused a substantial decrease in irinotecan and SN-38 AUCs as described in some case reports[38]—in combination with irinotecan treatment may have necessitated dose adaptation of either agent.

Although agreement on the classification results of the interactions by the panel was substantial, inconsistencies cannot be excluded between the significance scale used and the professional judgment of the panel members.[45] Therefore, the sensitivity of this scale according to *Drug Interaction Facts*[7] needs to be properly validated.

CONCLUSIONS

The present study revealed that during treatment of metastatic colorectal cancer using irinotecan or oxaliplatin, or both, a diverse group of comedication agents was prescribed for patients. Based on a literature review, 11 clinically significant interactions were identified with irinotecan and 1 nonspecific, clinically significant interaction with oxaliplatin, according to the classification by a panel of medical oncologists and clinical pharmacists. In the patient group that was studied, the occurrence of these clinically significant interactions was low: 1 interaction with phenytoin may have affected the efficacy of irinotecan treatment. Therefore, in clinical practice, the significance of interactions with irinotecan and oxaliplatin is limited, but the interactions that are classified as clinically significant should be recommended for (electronic) medication surveillance.

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Address correspondence to: Frank G.A. Jansman, PharmD, Groningen University Institute for Drug Exploration (GUIDE), Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Antonius Deusinglaan 1, 9713 AV Groningen, the Netherlands. E-mail: f.g.a.jansman@isala.nl