

Potential Interactions with Anticancer Agents: A Cross-Sectional Study

A. Mouzon^a J. Kerger^b L. D'Hondt^b A. Spinewine^{a, c}

Departments of ^aPharmacy and ^bMedical Oncology, CHU Mont-Godinne Dinant, Université catholique de Louvain, Yvoir, and ^cClinical Pharmacy Research Group, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

Key Words

Oncology · Antineoplastic agents · Drug interactions · Observational study

Abstract

Background: Patients with cancer are particularly susceptible to drug interactions (DIs), but the extent of the problem has received limited attention. We aimed to evaluate the frequency of interactions with anticancer agents in a group of cancer patients. **Methods:** The study was performed in a Belgian teaching hospital. One hundred and twenty-two patients with solid malignancies were included. A comprehensive drug history was performed by a clinical pharmacist. Three renowned DI compendia were used to identify DIs. **Results:** Forty-one potential interactions involving an anticancer agent and considered to be clinically significant were identified among 25% of patients. The anticancer drugs mostly involved were cisplatin and methotrexate, and the most frequent co-medications involved were vitamin K antagonists, proton pump inhibitors and diuretics. In the majority of cases, the potential adverse consequence was increased toxicity of the anticancer agent and/or of the co-medication. Less than 10% of DIs were identified by the three compendia. **Conclusions:** Preventive measures should be taken to avoid

increased toxicity or decreased efficacy of the drugs. Most of the time, this simply involves surveillance of biological or clinical parameters. Collaboration with a clinical pharmacist may be useful for the prescribing physician.

© 2013 S. Karger AG, Basel

Introduction

Cancer patients are particularly susceptible to drug interactions (DIs) for several reasons. Many of them are ≥65 years old, have several comorbidities and frequently take many medications [1]. The risk of interactions is further increased by (1) multiple prescribers for a single patient [2], and (2) the use, often without the awareness of prescribers, of over-the-counter (OTC) drugs, herbs or vitamins [3].

Anticancer agents usually have a narrow therapeutic index, and therefore, a slight increase or decrease in cytotoxic activity due to a DI can have major consequences [3]. An observational study using medical records and autopsy analysis showed that 4% of deaths among cancer patients were caused by chemotherapy itself, and serious drug-drug or drug-disease interactions were sometimes suspected [4].

Renowned databases [5–7] and literature reviews [3, 8–11] display dozens of DIs involving anticancer drugs. For example, fluorouracil can increase the anticoagulant effect of coumarins [3, 9], cotrimoxazole or pantoprazole may increase the toxicity of methotrexate [8, 12], and even fatal cases of fluorouracil or methotrexate toxicity have been reported in patients who receive sorivudine or non-steroidal anti-inflammatory drugs (NSAIDs), respectively [3, 8]. Interactions can also occur with food, alcohol or herbs. For example, some components of grapefruit juice can increase the bioavailability of drugs through inhibition of the cytochrome P450 3A4 [13], St. John's wort may accelerate the metabolism of imatinib [14], and alcohol may increase the toxicity of methotrexate [15].

Therefore, the risk of DIs in cancer patients is important to consider and has been the object of several studies [16–22]. A recent systematic review found that approximately one third of ambulatory cancer patients had potential DIs, but only limited data were found on the clinical consequences of DIs [10]. Individual studies had important weaknesses. First, most studies were retrospective in nature. Second, none of them used more than one source of information to detect DIs, although there is good evidence that no single source has sufficient sensitivity to detect DIs [23–27]. Third, previous studies did not take into account interactions with complementary or alternative medications, herbs or food.

The objective of this study was to evaluate, in a group of cancer patients, the frequency of clinically relevant interactions between anticancer agents and any of the following: other prescribed drug, other anticancer agent, OTC drugs, herbs, vitamins, grapefruit juice, alcohol or tobacco. Secondary objectives were to identify the types of drugs mostly involved and to describe adverse consequences and management.

Methods

The study was conducted at CHU Mont-Godinne (Yvoir, Belgium), a 421-bed teaching hospital, from November 2008 to January 2009 (9 weeks). The study was approved by the local Ethics Committee. All patients with a solid tumor and receiving chemotherapy were eligible. Patients were included if, during the study period, they came to the day hospital to be administered an intravenous product (mostly their chemotherapy, and in a few cases disphosphonates or albumin) or if they were admitted to the oncology ward. Patients who did not take any drug in addition to their chemotherapy regimen or with only short-term treatment linked to chemotherapy (such as a setron or glucocorticoids) were excluded. Each patient provided oral informed consent. As the

study was observational in nature, written consent was not required.

For each patient included, a clinical pharmacist performed a detailed drug history with the patient, using a piloted structured questionnaire (available upon request). The objective was to precisely identify all drugs taken by the patient in addition to the chemotherapy regimen (named 'co-medications' in this paper), including the following: prescribed drugs, OTC drugs, plants and vitamins. In addition, the clinical pharmacist collected the following data from the electronic health record and through patient interview: age, type of cancer, chemotherapy regimen, tobacco, alcohol and coffee consumption, contact details of the general practitioner (GP) and the community pharmacist. When patients could not remember all their medications and if they agreed, the community pharmacist was called, and when necessary, the GP could also be contacted. Sometimes the patients themselves provided additional information when they were back home.

The clinical pharmacist then searched for DIs with each anticancer agent taken by each patient. All anticancer agents were taken into account, irrespective of the type of agent (e.g., monoclonal antibodies and protein kinase inhibitors were also included), route of administration (i.e. intravenous as well as oral agents were considered) and day(s) of administration. Three DI sources were used: Micromedex® Healthcare Series online, Epocrates® online (free version) and Stockley's® Drug Interactions [5–7]. These sources were selected because they have good performance rankings in terms of sensitivity, specificity, completeness or ease of use [23, 28–31]. A selection of the most clinically relevant DIs was done. Micromedex classifies DIs into 5 categories of severity: contraindicated, major, moderate, minor, and unknown. For this study, only the first 3 were selected. In Epocrates, DIs are classified as 'contraindicated', 'avoid/use alternative', 'monitor/modify treatment', 'therapeutic advantage', and 'caution advised'. Only the first 3 classes were selected. In Stockley's, there is no explicit ranking system in terms of clinical significance, severity or level of evidence. Using the narrative text describing each interaction, we excluded DIs described as 'unlikely' or 'of minor clinical significance'.

All interactions described in at least one of the aforementioned sources were recorded. Prevalence was calculated, and a descriptive analysis of the characteristics of DIs was done with regard to drugs involved, severity, adverse consequences, management, and source of information.

Results

During the study period, 136 patients with a solid tumor and receiving chemotherapy were evaluated for inclusion. Fourteen patients were excluded because they had no co-medications or only a short-term treatment linked to chemotherapy. The characteristics of patients included ($n = 122$) are described in table 1. The mean age was 63 years (range 29–85). Patients took an average of 7.5 co-medications (range 1–22).

A total of 41 potential interactions considered as clinically significant were identified. Thirty patients (24.6%) had at least 1 interaction involving their anticancer

Table 1. Characteristics of patients (n = 122)

Demographics	
Age, years	63.4 ± 10.9
Age ≥ 65 years	58 (47.5)
Women	59 (48.4)
Outpatients	105 (86.1)
Type of cancer	
Gastrointestinal	34 (27.9)
Lung	29 (23.8)
Breast	27 (22.1)
Genitourinary	10 (8.2)
Gynecologic	5 (4.1)
Skin	4 (3.3)
Brain	2 (1.6)
Miscellaneous	11 (9)
Anticancer agents most frequently used ¹	
Fluorouracil	35 (28.7)
Cisplatin	27 (22.1)
Gemcitabine	19 (15.6)
Docetaxel	17 (13.9)
Cyclophosphamide	15 (12.3)
Irinotecan	13 (10.7)
Epirubicin	11 (9.0)
Drugs used (other than chemotherapy)	
Prescribed drugs	5.3 ± 3.2
≥ 5 prescribed drugs	63 (51.6)
≥ 10 prescribed drugs	11 (9.0)
OTC drugs	1.4 ± 1.1
≥ 1 OTC drug	98 (80.3)
Plants/vitamins	0.7 ± 1.3
≥ 1 plant/vitamin	44 (36.1)
Total co-mediations	7.5 ± 3.7

Values are means ± standard deviation or n (%). Co-mediations include all drugs taken by the patient in addition to the chemotherapy regimen.

OTC = Over-the-counter. ¹ Some patients received more than 1 anticancer agent.

agent(s), 9 patients (7.4%) had 2 interactions and 1 patient (0.8%) had 3 interactions. Beside interactions between two anticancer agents, 23 patients (18.9%) had at least 1 interaction involving their usual therapy.

The characteristics of DIs are presented in table 2. Among the 18 interactions described in Micromedex, 10 (55.6%) were considered as of major severity and 11 (61.1%) got an excellent documentation. In contrast, only 2 (10%) of the 20 interactions found with Epocrates were set in the 'contraindicated' or 'avoid/use alternative' group. Only 7% of interactions were reported in the three sources, and 66% were reported in only one of the three sources. Potential adverse consequences were far more

Table 2. Characteristics of interactions (n = 41)

<i>Drug involved</i>	
Between an anticancer agent and a prescribed drug	23 (56.1)
Between two anticancer agents	10 (24.4)
Between an anticancer agent and miscellaneous products ¹	7 (17.1)
Between an anticancer agent and an OTC drug	1 (2.4)
<i>Significance</i>	
According to Micromedex (n = 18)	
Considered as major interactions ²	10
Considered as moderate interactions ³	8
According to Epocrates (n = 20)	
Considered as 'contraindicated' or 'avoid/use alternative'	2
Considered as 'monitor/modify treatment'	18
<i>Adverse consequences</i>	
Increased toxicity of both drugs	14 (34.1)
Increased toxicity of anticancer agent	11 (26.8)
Increased toxicity of co-medication	9 (22)
Decreased efficacy of anticancer agent	6 (14.6)
Decreased efficacy of co-medication	1 (2.4)
<i>Management (as recommended in the sources used)</i>	
Monitoring	26 (63.4)
Avoid interaction	6 (14.6)
Change dosage	4 (9.8)
Substitute for another drug	3 (7.3)
Nothing suggested	2 (4.9)
<i>Sources of information</i>	
Interactions found in the 3 sources	3 (7.3)
Interactions found in only 1 source	27 (65.9)
Interactions found only in Micromedex	5 (12.2)
Interactions found only in Epocrates	13 (31.7)
Interactions found only in Stockley's	9 (22)

Values are n (%).

¹ Tobacco, alcohol, grapefruit juice, caffeine, vitamin (folic acid).

² Major: the interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse effect.

³ Moderate: the interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy.

often increased toxicity than decreased efficacy. For interactions between an anticancer agent and a drug taken for a different purpose, the affected drug was the latter in two third of cases and the anticancer agent in one third of cases. With regard to management, most of the time surveillance was required and sufficient. Sixteen DIs (39.0%) were pharmacodynamic and 22 (53.7%) were pharmacokinetic in nature. Three (7.3%) interactions had an unknown mechanism.

Table 3. Description of interactions

Interactions	Pa- tients	Mechanism (PD or PK)	Outcome	Management, severity rating, level of evidence (if available)
Capecitabine + coumarin	2	PK	May increase INR, risk of bleeding	<ul style="list-style-type: none"> - Patient should be closely and regularly monitored for alterations in their PT or INR; adjustments of coumarin dose may be necessary (Micromedex: M-E) - Monitor INR (Epocrates: M/m) - PT or INR should be regularly monitored anticipating the need to reduce the coumarin dose (Stockley's)
Carboplatin + furosemide	2	PD	May increase risk of ototoxicity, electrolyte abnormalities	Monitor renal function, electrolytes (Epocrates: M/m)
Cisplatin + vinorelbine	3	PD	May increase risk of granulocytopenia	<ul style="list-style-type: none"> - Patients should be monitored for signs and symptoms of myelosuppression, specifically grade 3 and 4 granulocytopenia (Micromedex: M-E) - Caution advised, monitor CBC (Epocrates: M/m)
Cisplatin + amiodarone	1	PD	May increase risk of QT prolongation, cardiac arrhythmias (hypokalemia)	Monitor potassium, electrolytes (Epocrates: M/m)
Cisplatin + bleomycine	1	PK	May increase risk of Raynaud's phenomenon; may increase bleomycin levels, risk of toxicity	<ul style="list-style-type: none"> - Caution advised, monitor renal function (Epocrates: M/m) - Concurrent use should be very closely monitored and renal function checked (Stockley's)
Cisplatin + docetaxel	3	PD	May increase risk of neuropathy	Monitor patients for signs of peripheral neuropathy (Micromedex: m/E)
Cisplatin + fenofibrate	1	PK	May increase fenofibrate levels, risk of myopathy	Caution advised, monitor renal function (Epocrates: M/m)
Cisplatin + haloperidol	1	PD	May increase risk of QT prolongation, cardiac arrhythmias	Monitor potassium, electrolytes (Epocrates: M/m)
Cisplatin + methotrexate	1	PK	May severely increase toxicity of methotrexate	The serum methotrexate levels should be closely monitored so that any delay in its clearance is detected early and folic acid rescue therapy can be given (Stockley's)
Cisplatin + salmeterol	1	PD	May increase risk of hypokalemia	Monitor potassium (Epocrates: M/m)
Etoposide + grapefruit juice	1	PK	May unexpectedly result in reduced blood levels of etoposide	Avoid concomitant use of etoposide and grapefruit juice until this potential interaction is better understood (Micromedex: m/G)
Etoposide + valproate	1	PK	May decrease plasma level of valproate, risk of tonic-clonic seizure	Avoid concurrent use or closely monitor serum antiepileptic levels making dosage adjustments as necessary and monitor the efficacy of the antineoplastic (Stockley's)
Fluorouracil + coumarin	1	PK	May result in an increased risk of bleeding	<ul style="list-style-type: none"> - In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR should be closely monitored with the addition and withdrawal of treatment with fluorouracil and should be reassessed periodically during concurrent therapy; adjustments of the anticoagulant dose may be necessary in order to maintain the desired level of anticoagulation (Micromedex: M-E) - PT or INR should be regularly monitored anticipating the need to reduce the coumarin dose (Stockley's)
Fluorouracil + folic acid	1	PD	May increase fluorouracil toxicity	Patient should not be given folic acid, should be told to avoid multivitamin preparation with folic acid (Stockley's)
Fluorouracil + hydrochlorothiazide	2	Unknown	May result in myelosuppression (granulocytopenia)	<ul style="list-style-type: none"> - Monitor closely for myelosuppression, by obtaining periodic CBCs (Micromedex: m-F) - Not specified (Stockley's)

Table 3 (continued)

Interactions	Pa- tients	Mechanism (PD or PK)	Outcome	Management, severity rating, level of evidence (if available)
Irinotecan + tobacco	2	PK	May decrease irinotecan concentrations	Specific dosing adjustments or recommendations cannot be made at this time; monitor patients smoking cigarettes while receiving irinotecan closely for loss of irinotecan efficacy (Micromedex: M-E)
Lapatinib + fentanyl	1	PK	May increase fentanyl levels, risk of prolonged/severe CNS and respiratory depression, other adverse effects; may delay recovery from fentanyl anesthesia	Caution advised, consider lower fentanyl doses (Epocrates: M/m)
Lapatinib + alprazolam	1	PK	May increase BZD levels, risk of CNS depression, psychomotor impairment	Caution advised, consider lower BZD doses (Epocrates: M/m)
Lapatinib + enalapril/ hydrochlorothiazide	1	PD	May increase risk of QT prolongation, cardiac arrhythmias (hypokalemia)	Monitor potassium, electrolytes (Epocrates: M/m)
Lapatinib + warfarin	1	PK	May increase INR, risk of bleeding	Monitor INR (M/m)
Methotrexate + alcohol	1	PD	May result in increased hepatotoxicity	Patients taking methotrexate should minimize or avoid the consumption of ethanol (Micromedex: m-F)
Methotrexate + caffeine	1	PD	May decrease methotrexate efficacy	Avoid excessive consumption of caffeine and theophylline-containing drinks (Stockley's)
Methotrexate + (es)omeprazole	2	PK	May increase risk of methotrexate toxicity	<ul style="list-style-type: none"> - Omeprazole may have to be temporarily discontinued during methotrexate administration to avoid the potential for methotrexate toxicity, or closely monitor patients (Micromedex: M-G) - PPI should be discontinued 4-5 days before methotrexate administration; ranitidine may be a suitable alternative (Stockley's)
Methotrexate + pantoprazole	1	PK	May increase plasma concentration of the methotrexate metabolite, 7-hydroxymethotrexate, causing increased methotrexate side effects	<ul style="list-style-type: none"> - Use ranitidine instead of pantoprazole or monitor patients for increased methotrexate toxicity, particularly for effects such as myalgia and bone pain (Micromedex: m-G) - PPI should be discontinued 4-5 days before methotrexate administration; ranitidine may be a suitable alternative (Stockley's)
Paclitaxel + carboplatin	1	Unknown	May increase neurotoxicity	Not specified (Stockley's)
Paclitaxel + trastuzumab	1	PK	May increase trastuzumab levels	Monitor toxicity (Epocrates: M/m)
Pemetrexed + NSAIDs (here aceclofenac or ibuprofen, short half-life and creatinine clearance fluctuating between 76 and 92 ml/min)	1	PK	May result in pemetrexed toxicity (myelosuppression, renal toxicity and gastrointestinal toxicity)	<ul style="list-style-type: none"> - Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of and 2 days following administration of pemetrexed; if concomitant administration of an NSAID is necessary, monitor patients for toxicity, especially myelosuppression, renal toxicity, and gastrointestinal toxicity (Micromedex: M-F) - Avoid short-acting NSAID 2 days before until 2 days after pemetrexed dose in patients w/ CrCl <80 ml/min (Epocrates: A/u) - Caution when pemetrexed is used with high doses of NSAIDs if renal function is normal, or avoid for 2 days before, the day of and for 2 days after pemetrexed use in patients with mild to moderate renal impairment (Stockley's)
Pemetrexed + fenofibrate	1	PK	May increase fenofibrate levels, risk of myopathy	Caution advised, monitor renal function (Epocrates: M/m)

Table 3 (continued)

Interactions	Pa-tients	Mechanism (PD or PK)	Outcome	Management, severity rating, level of evidence (if available)
Procarbazine + alcohol	1	PK	May result in flush	Patient should be warned that this can be more embarrassing and frightening than serious; it is best to avoid alcohol (Stockley's)
Procarbazine + tramadol	1	PD	May increase risk of serotonin syndrome, seizures	Contraindicated within 14 days of MAO inhibitor use (Epocrates; CI)
Sorafenib + proton pump inhibitor	1	PK	May reduce the solubility of sorafenib	Avoid chronic treatment with PPI during treatment with sorafenib (Stockley's)
Vincristine + phenobarbital	1	PK	May increase clearance of vincristine, greater relapse	Not specified (Stockley's)

PD = Pharmacodynamic; PK = pharmacokinetic; INR = international normalized ratio; PT = prothrombin time; CBC = complete blood count; CNS = central nervous system; BZD = benzodiazepine; PPI = proton pump inhibitor; w/CrCl = with creatinine clearance; MAO = monoamine oxidase; A/u = avoid/use alternative; CI = contraindicated; M/m = monitor/modify treatment. For Micromedex: E = excellent documentation; F = fair documentation; G = good documentation; M = major interaction; m = moderate interaction.

The anticancer drugs mostly involved in interactions were cisplatin (n = 12, including 8 with another anticancer agent), methotrexate (n = 6, including 1 with another anticancer agent), lapatinib (n = 4), and fluorouracil (n = 4). The most frequent co-medications interacting with chemotherapy were diuretics (n = 5), vitamin K antagonists (n = 4), proton pump inhibitors (n = 4), anticonvulsants (n = 2), and lipid-modifying agents (n = 2). The only OTC drug and the only vitamin involved in an interaction were an NSAID and folic acid. Proton pump inhibitors were not available as OTC drugs at the time of the study.

A detailed description of the 41 interactions is provided in table 3.

Discussion

The present study shows that almost 25% of patients had at least 1 interaction of clinical significance involving their anticancer agent(s). Even after discounting interactions between two anticancer drugs, an interaction was still detected in 19% of patients.

Although direct comparison is difficult, the incidence seems to be higher than in previous studies. One study that focused on oxaliplatin and irinotecan found a clinically significant DI in 12% of patients [18]. Another study that focused on pharmacokinetic interactions affecting the activity of the anticancer agent found a 5% prevalence rate [20]. Other studies found similar [10, 16–17] or higher [19, 21] rates of DIs, but the interactions considered were not limited to DIs with anticancer agents.

This high incidence might be a consequence of our attempt to maximize sensitivity. This was done in two ways. First, special attention was paid to obtain comprehensive drug history. Second, three different sources were used to identify DIs. Many studies have shown discrepancies in listing and rating systems between different DI sources [23–26]. The three sources selected – even if they are renowned and widely used worldwide [23, 26, 31] – are no exception to the rule. Only 3 (7.3%) interactions were reported in the three sources and 27 (65.9%) were reported in only one of them. This highlights the need to use a combination of sources of information, even when focusing on clinically significant interactions.

One fourth of DIs involved two anticancer agents. These combinations usually belong to validated protocols, and adverse effects are usually carefully monitored by oncologists.

In contrast, more than half of the interactions involved a prescribed drug other than an anticancer agent. The in-

teracting drugs were almost always prescribed by different prescribers (e.g., an oncologist and a GP). This increases the risk of not detecting the interaction, and therefore, the risk of an adverse drug event (ADE).

Similarly to previous studies, the use of complementary medicines or products was frequent [32, 33]. Prescribers are often unaware of their use for several reasons: for example, because patients fear disapproval [3, 8, 34, 35]. Nevertheless, the prevalence of interactions with OTC drugs, plants and vitamins was found to be low. This could be due to the low sensitivity of the sources used, at least for DIs with plants. In fact, no interaction involving a plant was detected with any of the three sources used, but a separate search in two specific sources of information [36, 37] identified 2 DIs with plants (garlic inducing the metabolism of etoposide, and black cohosh increasing the toxicity of paclitaxel). Stockley's Herbal Medicine Interactions textbook was not available at the time of the present study, but could be used in future studies [38].

Different recommendations can be made to decrease the risk of DIs in clinical practice.

First, oncologists and GPs should pay special attention when prescribing drugs more likely to interact. The need for co-medication has to be reassessed. If both drugs are necessary, most of the time, clinical or biological surveillance is required. Some doses might need adjustment (e.g., coumarins, fentanyl), and in some cases, the co-medication (e.g., NSAIDs) can be temporarily discontinued. If the latter is not possible, the drug can be replaced by another drug with a lower potential to interact (e.g., ranitidine instead of proton pump inhibitors) [5, 11, 39, 40]. Although these options seem relatively easy to implement in practice, oncologists are often reluctant to apply them [41]. They acknowledge little communication with pharmacists and have confidence in their ability to manage various degrees of toxicity.

Second, clinical pharmacists can contribute to better prevention and detection in different ways [12, 37]. They can compound educational tools for prescribers, answer specific questions asked by prescribers or even play a proactive role by checking each patient's therapy.

Third, patients themselves should be aware of the risk of DIs. They should keep an updated list of their medications and present this list to each doctor they see [42], they should not practice self-medication without talking to their doctor and ought to pay attention to the warning signs of ADEs [11].

Fourth, the classifications of the severity and scientific evidence of DIs in existing sources of information should be standardized to minimize confusion [24].

Finally, automated detection of DIs through computerized prescribing order entry and clinical decision support systems could be valuable to better detect DIs. However, this would require sharing prescription data across care settings. Unfortunately, this is currently not available in most cases.

The present study has several limitations. First, similarly to previous studies [16–18, 20, 41], we did not evaluate the clinical impact of DIs. A longitudinal cohort design and a larger sample would have been required. Nevertheless, we excluded DIs of minor clinical significance. Even though not all patients taking two interacting drugs will experience an ADE, harmful consequences must not be neglected [43]. In the present study, a patient taking warfarin had her international normalized ratio rising to 8.2, following the use of capecitabine and lapatinib. Second, the study was monocentric. However, the center has large activities in oncology, and the patients included were cared for by several oncologists. Third, the prevalence of DIs might have been underestimated, because few patients were taking a tyrosine kinase inhibitor or methotrexate, two drugs with a large potential to interact. A new study including patients with hematological cancers could provide valuable information.

In conclusion, this study confirms that most cancer patients take many drugs besides their chemotherapy and shows that a fourth of patients have at least 1 DI of clinical relevance. Unfortunately, little is known about the prevalence of ADEs due to these interactions. Despite this, it is essential that preventive measures are taken to avoid increased toxicity or decreased efficacy of the drugs. Most of the time, this simply involves surveillance of biological or clinical parameters. Collaboration with a clinical pharmacist might also be useful. An educational leaflet focusing on the most frequent and relevant DIs identified in the present study has been made available for prescribers.

Acknowledgments

We thank all patients and oncologists who participated in the study. We thank J.D. Hecq, L. D'Hondt and P. Gillet for their support and for facilitating the conduct of this study.

Disclosure Statement

The authors declare that they have no conflict of interest.

References

- Hanigan MH, Dela Cruz BL, Thompson DM, Farmer KC, Medina PJ: Use of prescription and nonprescription medications and supplements by cancer patients during chemotherapy: questionnaire validation. *J Oncol Pharm Pract* 2008;14:123–130.
- Green JL, Hawley JN, Rask KJ: Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? *Am J Geriatr Pharmacother* 2007;5:31–39.
- Blower P, de Wit R, Goodin S, Aapro M: Drug-drug interactions in oncology: why are they important and can they be minimized? *Crit Rev Oncol Hematol* 2005;55:117–142.
- Buajordet I, Ebbesen J, Erikssen J, Brors O, Hilberg T: Fatal adverse drug events: the paradox of drug treatment. *J Intern Med* 2001;250:327–341.
- Stockley IH: *Stockley's Drug Interactions*. Chicago, Pharmaceutical Press, 2008.
- Thomson Reuters Micromedex® 1.0 (Healthcare series), 2009.
- Epocrates® online. 2009. <https://online.epocrates.com>.
- Beijnen JH, Schellens JH: Drug interactions in oncology. *Lancet Oncol* 2004;5:489–496.
- Riechelmann RP, Saad ED: A systematic review on drug interactions in oncology. *Cancer Invest* 2006;24:704–712.
- Riechelmann RP, Del Giglio A: Drug interactions in oncology: how common are they? *Ann Oncol* 2009;20:1907–1912.
- Rédaction La Revue Prescrire: Eviter les effets indésirables par interactions médicamenteuses: comprendre et décider. *Rev Prescrire* 2006;26(suppl 278).
- Ranchon F, Vantard N, Gouraud A, Schwiertz V, Franchon E, Pham BN, Vial T, You B, Bouafia F, Salles G, Rioufol C: Suspicion of drug-drug interaction between high-dose methotrexate and proton pump inhibitors: a case report – should the practice be changed? *Chemotherapy* 2011;57:225–229.
- Uno T, Yasui-Furukori N: Effect of grapefruit juice in relation to human pharmacokinetic study. *Curr Clin Pharmacol* 2006;1:157–161.
- Smith P, Bullock JM, Booker BM, Haas CE, Berenson CS, Jusko WJ: The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 2004;24:1508–1514.
- Neuman MG, Cameron RG, Haber JA, Katz GG, Malkiewicz IM, Shear NH: Inducers of cytochrome p450 2e1 enhance methotrexate-induced hepatotoxicity. *Clin Biochem* 1999;32:519–536.
- Riechelmann RP, Tannock IF, Wang L, Saad ED, Taback NA, Krzyzanowska MK: Potential drug interactions and duplicate prescriptions among cancer patients. *J Natl Cancer Inst* 2007;99:592–600.
- Riechelmann RP, Zimmermann C, Chin SN, Wang L, O'Carroll A, Zarinehbab S, Krzyzanowska MK: Potential drug interactions in cancer patients receiving supportive care exclusively. *J Pain Symptom Manage* 2008;35:535–543.
- Jansman FG, Idzinga FS, Smit WM, de Graaf JC, Coenen JL, Sleijfer DT, Brouwers JR: Classification and occurrence of clinically significant drug interactions with irinotecan and oxaliplatin in patients with metastatic colorectal cancer. *Clin Ther* 2005;27:327–335.
- Riechelmann RP, Moreira F, Smaletz O, Saad ED: Potential for drug interactions in hospitalized cancer patients. *Cancer Chemother Pharmacol* 2005;56:286–290.
- Lemachatti J, Leveque D, Beretz L, Bergerat JP: Potential pharmacokinetic interactions affecting antitumor drug disposition in cancer patients. *Anticancer Res* 2009;29:4741–4744.
- van Leeuwen RW, Swart EL, Boom FA, Schuitemaker MS, Hugtenburg JG: Potential drug interactions and duplicate prescriptions among ambulatory cancer patients: a prevalence study using an advanced screening method. *BMC Cancer* 2010;10:679.
- Girre V, Arkoub H, Puts MT, Vantelon C, Blanchard F, Droz JP, Mignot L: Potential drug interactions in elderly cancer patients. *Crit Rev Oncol Hematol* 2011;78:220–226.
- Vonbach P, Dubied A, Krahenbuhl S, Beer JH: Evaluation of frequently used drug interaction screening programs. *Pharm World Sci* 2008;30:367–374.
- Wong CM, Ko Y, Chan A: Clinically significant drug-drug interactions between oral anticancer agents and nonanticancer agents: profiling and comparison of two drug compendia. *Ann Pharmacother* 2008;42:1737–1748.
- Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, Van Bergen RC, Lipton RB: Concordance of severity ratings provided in four drug interaction compendia. *J Am Pharm Assoc* 2004;44:136–141.
- Vitry AI: Comparative assessment of four drug interaction compendia. *Br J Clin Pharmacol* 2007;63:709–714.
- Wang LM, Wong M, Lightwood JM, Cheng CM: Black box warning contraindicated comedications: concordance among three major drug interaction screening programs. *Ann Pharmacother* 2010;44:28–34.
- Barrons R: Evaluation of personal digital assistant software for drug interactions. *Am J Health Syst Pharm* 2004;61:380–385.
- Claudson KA, Polen HH, Marsh WA: Clinical decision support tools: performance of personal digital assistant versus online drug information databases. *Pharmacotherapy* 2007;27:1651–1658.
- Claudson KA, Marsh WA, Polen HH, Seamon MJ, Ortiz BI: Clinical decision support tools: analysis of online drug information databases. *BMC Med Inform Decis Mak* 2007;7:7.
- Perkins NA, Murphy JE, Malone DC, Armstrong EP: Performance of drug-drug interaction software for personal digital assistants. *Ann Pharmacother* 2006;40:850–855.
- Sparreboom A, Cox MC, Acharya MR, Figg WD: Herbal remedies in the united states: potential adverse interactions with anticancer agents. *J Clin Oncol* 2004;22:2489–2503.
- Werneke U, Earl J, Seydel C, Horn O, Crichton P, Fannon D: Potential health risks of complementary alternative medicines in cancer patients. *Br J Cancer* 2004;90:408–413.
- McCune JS, Hatfield AJ, Blackburn AA, Leith PO, Livingston RB, Ellis GK: Potential of chemotherapy-herb interactions in adult cancer patients. *Support Care Cancer* 2004;12:454–462.
- Yeung KS, Gubili J: Clinical guide to herb-drug interactions in oncology. *J Soc Integr Oncol* 2007;5:113–117.
- Solimando DA: *Drug Information Handbook for Oncology*. Hudson, Lexi Comp, 2007.
- About herbs, botanicals and other products. Integrative Medicine Service, Memorial Sloan-Kettering Cancer Center, New York. <http://www.mskcc.org/aboutherbs>.
- Williamson E, Driver S, Baxter K: *Stockley's Herbal Medicines Interactions*, ed 2. London, Pharmaceutical Press, 2013.
- Mallet L, Spinewine A, Huang A: The challenge of managing drug interactions in elderly people. *Lancet* 2007;370:185–191.
- Bink S, De Troy E: Interactions during oncological therapy: workshop on oncology. Leuven, ESCP Leuven, 2008.
- Sokol KC, Knudsen JF, Li MM: Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. *J Clin Pharm Ther* 2007;32:169–175.
- Cancer patients at risk of drug interactions. *CA Cancer J Clin* 2007;57:258–259.
- Riechelmann RP: Drug combinations with the potential to interact among cancer patients. *Support Care Cancer* 2007;15:1113–1114.