

## Potential Pharmacokinetic Interactions Affecting Antitumor Drug Disposition in Cancer Patients\*

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**Abstract.** *Aim: The extent of potential pharmacokinetic drug-drug interactions affecting anticancer agents disposition has not been specifically investigated. The prevalence of this type of interaction in adult ambulatory patients receiving systemic chemotherapy in our institution was examined. Patients and Methods: The medication list of 200 consecutive cancer patients receiving intravenous chemotherapy was prospectively collected by means of the prescriptions (chemotherapy, supportive care, medications for comorbidities) and a questionnaire (over-the-counter products). Interacting drugs had to have been taken in the previous 7 days. Data concerning the type of cancer and the nature of the comorbidities were also collected. Potential pharmacokinetic drug interactions affecting the activity of the anticancer agent were identified using the guide of drug interactions of the French drug agency (June 2007) and the literature. Results: A total of 200 patients (mean age 60 years; range 17-96 years) entered the study and 73.5% were female. The most common cancer types were breast cancer (41%), non-Hodgkin's lymphomas (17.5%), and gastrointestinal tumors (12.5%). The majority of the patients (58.5%) had a comorbid illness (cardiovascular diseases, hypothyroidism, diabetes, depression). The median number of medications per patient was 4 (range 1-14). All the patients received systemic chemotherapy but 29 (14.5%) also took anticancer drugs at home. Nine potential pharmacokinetic interactions were found in nine patients (frequency: 4.5%; 95% confidence interval: 1.6-7.4%). Most of the interactions (7/9) involved fluconazole that might alter the metabolism of oxazaphosphorines or the*

*elimination of bortezomib and paclitaxel. One association was contraindicated. Five interactions were not associated with a published clinical effect. No interaction with an enzyme or drug transporter inducer (e.g., rifampin, St. John's wort) was encountered. Conclusion: The frequency of potential pharmacokinetic interactions affecting the disposition of antitumor drugs was low in this population of ambulatory adult cancer patients and mostly involved the antifungal agent fluconazole.*

Drug-drug interactions (*i.e.* the modification of the pharmacological properties of a drug by a co-administered agent) are a major concern in therapy. In the United Kingdom, during the years 2001-2002, such interactions accounted for 16.6% of hospital admissions related to adverse drug reactions (1). In terms of mechanisms, drug-drug interactions may be pharmacodynamic (in relation to the mechanism of action of the drug) or pharmacokinetic (in relation to drug disposition). They are also classified either as potential, based on those identified (theoretical or real) by the analysis of prescriptions or as established following the observation of an unexpected clinical effect or drug concentration alterations. Drug-drug interactions have various levels of severity ranging from the absence of clinical significance to death that lead to no modification of treatment or to the contraindication of the combination.

Cancer patients are at high risk of drug-drug interactions since they take many medications (anticancer agents, drugs for supportive care and comorbidities, over-the-counter products). Anticancer agents may alter the pharmacological properties of co-administered drugs, but also the reverse (co-administered drugs have the potential to modify the activity of anticancer agents). Paradoxically, the importance of drug-drug interactions in cancer patients is little documented. In a Brazilian study, 63 out of 100 hospitalized cancer patients were found to present at least a potential drug-drug interaction (2). In addition, 38% of the interactions were classified as severe. Unfortunately, in this retrospective study, anticancer agents were excluded. The same team performed, in a Canadian hospital, a similar, but prospective study that included 405 ambulatory cancer patients receiving chemotherapy (3). Among the 36 potential

\*Presented in part at the 99th Annual Meeting of the American Association for Cancer Research (AACR), San Diego, 12-16 April 2008, and at the Annual Meeting of the American Association of Pharmaceutical Scientists (AAPS), Atlanta, 15-20 November 2008.

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**Key Words:** Anticancer agents, pharmacokinetic interactions.

Table I. Potential pharmacokinetic interactions affecting anticancer drug disposition in a population of 200 ambulatory patients (n=9).

Interacting drug (pharmacological class)	Anticancer agent	Mechanism of interaction	Number of cases	Published clinical effect
Fluconazole (antifungal agent)	Cyclophosphamide	Inhibition of metabolism	4	Yes
Fluconazole (antifungal agent)	Ifosfamide	Inhibition of metabolism	1	No
Fluconazole (antifungal agent)	Paclitaxel	Inhibition of metabolism	1	No
Fluconazole (antifungal agent)	Bortezomib	Inhibition of metabolism	1	No
Norflxacin (antibacterial agent)	Paclitaxel	Inhibition of metabolism	1	No
Verapamil (cardiovascular agent)	Irinotecan	Inhibition of metabolism	1	No

interactions that involved an anticancer agent, 27 were classified as pharmacokinetic and only 5 (1.2%) were associated with a potential modification of the activity of the anticancer agent (the remaining 31 were related to the modification of the activity of the non-oncological drug) (3). In a population of 122 adult patients treated by fluorouracil and leucovorin in the Netherlands, 4 (3.2%) patients were co-treated by a drug that potentially interacts with the anticancer agent (4).

Given the low therapeutic index of anticancer agents, we believe that it could be interesting to specifically evaluate the potential impact of co-administered drugs on anticancer agent activity in relation to a pharmacokinetic interaction. For intravenous anticancer drugs, pharmacokinetic interactions mainly occur during the elimination phase and result in increased or decreased drug exposure (area under the serum concentration-time curve or AUC). Interactions are due to the inhibition of molecular pharmacokinetic determinants (enzymes such as the cytochrome P450 superfamily, drug transporters such as P-glycoprotein) or induction (increased expression of these determinants) (5). The extent of potential pharmacokinetic drug-drug interactions affecting anticancer agents disposition in adult ambulatory patients receiving intravenous chemotherapy in our institution was examined. Most of the chemotherapies were administered on an out patient basis and this type of patient was considered to be representative of the cancer population under antitumoral treatment.

## Patients and Methods

The study took place at the haematology-oncology department of the university hospital of Strasbourg, France. All types of cancer are treated in the department except lung tumours. The complete medication list of 200 consecutive ambulatory adult cancer patients receiving intravenous chemotherapy was prospectively collected by means of the prescriptions (chemotherapy, supportive care, medications for comorbidities) and a questionnaire (over-the counter products). Patients treated by chemotherapy in the setting of a clinical trial were not considered.

The non-anticancer agents that were administered in the previous 7 days were considered as interacting drugs to take into account the maximal effect of drug metabolism and transport inducers (*e.g.*, rifampin). The anticancer drugs whose disposition was potentially affected were conventional cytotoxic agents (*e.g.*, epirubicin), monoclonal antibodies (*e.g.*, rituximab) and hormonotherapy (*e.g.*, tamoxifen).

Data regarding the type of cancer and the nature of the comorbidities were collected by physicians. Potential pharmacokinetic drug interactions affecting the anticancer agent disposition were identified using the guide of interactions of the French drug agency (Afssaps, June 2007) and the medical literature using PubMed (June 2007) by two pharmacists.

## Results

During July and August 2007, a total of 200 patients (mean age 60 years; range 17-96 years) entered the study and 147 (73.5%) were female. The most common cancer types were breast cancer (41%), non-Hodgkin's lymphoma (17.5%), gastrointestinal tumours (12.5%) and genitourinary carcinoma (7%). The majority of the patients (58.5%) had a comorbid illness (cardiovascular disease, 20%; hypothyroidism, 10%; dyslipidaemia, 9.5%; diabetes, 7.5%; depression, 6.5%). The median number of medications (chemotherapy and non-anticancer drugs taken in the previous 7 days) per patient was 4 (range 1-14). All the patients received systemic chemotherapy but 29 (14.5%) also took anticancer drugs at home (hormonotherapy, capecitabine, chlorambucil).

Nine potential pharmacokinetic interactions were found in 9 patients (frequency: 4.5%; 95% confidence interval: 1.6-7.4%) (Table I). All the interactions were related to cytochrome P450 (CYP) inhibition. Most of the interactions (7/9) involved fluconazole (CYP3A4 and CYP2C9 inhibitor) that might alter the metabolism of cyclophosphamide (n=4) and ifosfamide (n=1) or the elimination of bortezomib (n=1) and paclitaxel (n=1). Other potential interactions were norflxacin (CYP3A4 inhibitor) with paclitaxel (n=1) and verapamil (CYP3A4 inhibitor) with irinotecan (n=1). Four interactions were associated with a published clinical effect (cyclophosphamide and fluconazole; decreased toxicity,

potential decreased activity) (8). One combination (irinotecan and verapamil) is contraindicated in France because of possible increased toxicity. Other interactions were associated with a theoretical clinical effect. No interaction with an enzyme or drug transporter inducer (*e.g.*, rifampin, St John's wort) was encountered.

## Discussion

The frequency of potential pharmacokinetic interactions affecting the disposition of antitumor drugs was low (4.5%) in the present population of ambulatory adult cancer patients. All the interactions were related to the inhibition of CYP mediated metabolism. Irinotecan is a prodrug partly eliminated *via* CYP3A4 metabolism. Combination of ketoconazole (the CYP3A4 inhibitor prototype) with irinotecan resulted in the doubling of the exposure to the cytotoxic entity (SN38) (6). Hence, to prevent any fatal outcome, the association of irinotecan with any CYP3A4 inhibitor (*e.g.*, verapamil) is contraindicated. The other potential pharmacokinetic interactions (7/8) mostly involved the antifungal agent fluconazole. Fluconazole is an inhibitor of CYP3A4 and CYP2C9 that may alter the metabolism of co-administered anticancer drugs (7). The oxazaphosphorines cyclophosphamide and ifosfamide are prodrugs that need CYP-mediated anabolism to produce the active phosphoramidate mustard. Fluconazole may enhance the exposure to cyclophosphamide (*i.e.* decrease the production of the active entity) that may lead to lower toxicity but also to a potential lower activity (8). Regarding ifosfamide, inhibition of CYP3A4 catabolism may reduce the formation of the active metabolite (9). In addition, fluconazole may delay paclitaxel and bortezomib elimination *via* inhibition of CYP3A mediated catabolism (10, 11). Similarly, norfloxacin (CYP3A4 inhibitor) may reduce the metabolism of paclitaxel (12).

Regarding the Canadian study performed in 2005-2006 in 405 adult ambulatory patients, the frequency of potential pharmacokinetic interactions involving the activity of an anticancer agent was also low (1.2%; 5/409) (3). However the profile of pharmacokinetic interactions was totally different. Four interactions concerned the association of ondansetron with cisplatin and one interaction was related to the effect of cimetidine on fluorouracil disposition (3). Although the types of patients and the dates of the studies were comparable, this discrepancy was not really surprising because the number of events was low. In addition, the clinical practices and the interpretation of interactions might have differed. In our institution, cisplatin is not administered in the ambulatory setting but in hospitalized patients and cimetidine is no longer used in practice. Regarding ondansetron, this antiemetic was not considered as an interacting drug because it was not used in the previous 7 days before chemotherapy.

The frequency of potential pharmacokinetic interactions overestimates the rate of real interactions because it takes into account both previously observed and theoretical interactions. In the present study, five potential interactions were not associated with a published clinical effect (fluconazole and ifosfamide; fluconazole and bortezomib; fluconazole and paclitaxel; norfloxacin and paclitaxel; verapamil and irinotecan). The risk of association was related to the possible CYP-mediated metabolism inhibition.

Potential pharmacokinetic drug-drug interactions are preventable since they can be identified before dispensing or administration *via* the analysis of prescriptions. However, their detection requires that the complete medication list is obtained by health professionals. This is not easy to achieve since some patients who have contact with several doctors do not have their complete medication reviewed (13). The *a priori* identification of interactions also necessitates the availability of updated and exhaustive compendia or databases and probably a good training in the mechanisms of drug-drug interactions.

Oral chemotherapy with recently approved tyrosine kinase inhibitors (*e.g.*, imatinib, sunitinib) is becoming important. These agents are administered chronically and based on what is known of their pharmacokinetic determinants, they have a high potential of pharmacokinetic interactions. We are currently investigating the frequency of potential pharmacokinetic drug drug interactions among ambulatory cancer patients taking oral anticancer agents. In conclusion, the extent of potential pharmacokinetic drug-drug interactions affecting anticancer agents disposition in adult ambulatory patients receiving intravenous chemotherapy was low.

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*Received May 22, 2009*

*Revised September 7, 2009*

*Accepted September 14, 2009*