review

Drug interactions in oncology: how common are they?

R. P. Riechelmann1* & A. Del Giglio2

1Internal Medicine, Federal University of Sao Paulo and 2Medical Oncology, ABC School of Medicine, Sao Paulo, Brazil

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Background: Drug–drug interactions (DDIs) comprise an important problem in medical oncology practice. We systematically reviewed the frequency of DDIs in oncology.

Methods: We searched PubMed for eligible articles and on-line databases for abstracts of major oncology meetings. Eight studies reported on the frequency of DDIs: six evaluated the frequency of potential DDIs, while two studies reported on real DDIs, i.e. interactions that had clinical consequences. Studies of potential DDIs found that approximately one-third of patients are exposed to dangerous drug doublets, with the most common ones involving warfarin and anticonvulsants. One study of real DDIs found that 2% of hospitalized cancer patients had a DDI as the cause of admission.

Conclusions: Drug interactions comprise an important issue in oncology, with approximately one-third of ambulatory cancer patients at risk of DDIs. Data are limited on the clinical consequences of drug interactions among cancer patients.

Key words: adverse effects, drug interactions, drug therapy, neoplasms

introduction

A drug–drug interaction (DDI) is defined as an increase or decrease in the clinical effect of a given drug due to interference by another drug [1]; they can occur between drugs and between drugs and food, herbs, formulation excipients/containers or environmental factors (such as tobacco) and are classified into three types: pharmacokinetic, pharmacodynamic and pharmaceutical [1]. DDIs comprise a significant cause of morbidity and mortality worldwide as they may lead to adverse clinical events, result in decrease/inactivation of the therapeutic effect of a drug, may enhance drug toxicity and indirectly compromise treatment outcomes and adherence.

Studies in general medicine have evaluated the frequency of adverse drug events, including drug interactions, among patients with various medical conditions. They have found frequency of potential drug interactions ranging from a low of 16% among emergency room patients to a high of 70% in a population of ambulatory patients being treated by their family physician [2, 3]. A large population study which analyzed >5 million prescriptions in the French health care identified 2% of outpatients who were prescribed either absolutely or relatively contraindicated drug combinations [4].

In theory, patients with cancer are particularly susceptible to DDIs because they frequently take many medications—to treat their cancer, to treat treatment-induced toxicity and cancer-related syndromes and to treat other comorbid illnesses [5]. In addition, their pharmacokinetic parameters may be distorted because of impaired absorption due to mucosites, increased volume of distribution resulting from edema and malnutrition and altered excretion secondary to organ dysfunction. However, the exact prevalence of DDIs among cancer patients is unknown. Because of different study designs, screening methods and study populations, the rates of potential drug interactions have varied in the literature.

We have made a systematic review on the epidemiology of DDIs in oncology.

methods

We searched PubMed for epidemiology articles related to DDI, i.e. articles describing the frequency of potential DDIs, of real DDIs and/or risk factors for DDIs among cancer patients. We initially used the medical subject headings ‘drug interactions’, ‘drug therapy, combination’ and ‘neoplasms’ published up to April 2009. Because >33 000 articles came up, we changed the search to use the title words ‘drug interactions’ AND ‘oncology’ and ‘drug interactions’ AND ‘cancer’, limiting the search to articles published in English, Portuguese and Spanish. We also sought relevant articles within the reference lists of publications selected for the primary search. We complemented the search with abstracts presented at the American Society of Clinical Oncology (ASCO) meetings from 2005 to 2008; this time span was selected because we considered that studies presented before 2005 were likely to be already published. We used the ASCO Web site electronic engine to look for eligible studies, utilizing the words ‘drug interaction’ or ‘drug interactions’ listed in the abstracts’ titles. Drug-food, drug-herb and drug-supplement interactions were beyond the scope of this review.

Descriptive statistics was used to describe the results, separated by potential versus real DDIs.
results

The primary search retrieved 25 articles (24 full articles from PubMed and one abstract from ASCO) and eight were considered eligible (Table 1). The results are described separately as (i) potential drug interactions, i.e. drug combinations with the potential to interact and (ii) real drug interactions, i.e. drug interactions that resulted in clinical and/or laboratory consequences. A summary of common examples of DDIs reported by the selected studies is listed in Table 2.

potential drug interactions in oncology

Six articles describing the epidemiology of potential DDIs in oncology were identified. All but one study were carried out in a single institution, and most used electronic methods to screen for potential DDIs. The frequency of potential DDIs varied from 12% to 63%, mainly depending on the type of study population. The main findings from these articles are summarized below and in Table 3.

A retrospective study evaluated 100 consecutive hospitalized patients with solid or hematologic malignancy who had not received anticancer therapy in the previous 4 weeks; they found that 63% of patients were exposed to at least one combination of drugs that could potentially interact [6]. The authors screened drugs for interactions using ‘Drug Interaction Facts’ software (electronic source: www.factsandcomparisons.com), which has been shown to have an accuracy of >95% in detecting previously known drug interactions [7]. The program classifies interactions by pharmacological mechanisms, levels of severity (major, when an interaction could offer risk of death; moderate, when the clinical consequence of an interaction required medical attention, or minor, when minimum clinical effect was expected from the combination of two drugs) and scientific evidence from the literature (rated in a five-point scale, where level 1 represents a drug interaction supported by clinical trials and level 5 means a theoretical risk for interaction). According to the Drug Interaction Facts classification, interactions were moderate or severe in 75% of the cases and the most common combinations with potential for interaction were opioids with benzodiazepines, selective serotonin reuptake inhibitors with opioids, nonsteroidal anti-inflammatory drugs with low-molecular-weight heparins (LMWHs), dexamethasone with phenytoin and omeprazole with benzodiazepines.

A prospective multicenter study assessed 98 consecutive colorectal cancer outpatients who were receiving systemic treatment with irinotecan- and/or oxaliplatin-based regimens with the aim of identifying potential DDIs involving such agents [8]. They searched PubMed and Excepta medica database (EMBASE) for known DDIs involving irinotecan and oxaliplatin and examined whether patients were taking those drug combinations with the potential to interact that were selected by the literature search. The authors used the Drug Interaction Facts program and also a panel of oncologists and pharmacists to classify DDIs in terms of clinical significance; the panel scored 12 clinically significant DDIs involving these agents. The study found that 71 irinotecan-treated patients were taking at least one drug that could potentially interact with this topoisomerase inhibitor, with the most common ones being loperamide (85% of the 71 patients), dexamethasone (60%) and phenytoin (one patient). Any significant potential DDI was identified among oxaliplatin-treated subjects [8].

A cross-sectional study surveyed 405 ambulatory adult patients with solid tumors who were receiving standard anticancer therapy, asking them about all medications taken by them for the previous 4 weeks [9]. Commercially available medications were screened for interactions by the same software utilized in their previous study. Among 405 patients, 276 combinations with the potential to interact were found in 109 (27%) patients. Nine percent of potential drug interactions were of major severity, 77% of moderate severity and 14% of minor severity; 53% of them were supported by level 1–3 scientific evidence (i.e. interactions supported by at least a few case reports). More than half (55%) of potential interactions were pharmacokinetic. Among all interactions, 240 (87%) involved either supportive care agents or medications to treat comorbid conditions and 36 (13%) involved anticancer drugs. The potential drug interactions between antineoplastic agents and general medications identified were warfarin associated with capetitabine, fluorouracil, carboplatin, gemcitabine or paclitaxel (15 cases), hydrochlorothiazide combined with fluorouracil and cyclophosphamide (six cases), quinolones combined with cyclophosphamide (five cases), ondansetron and cisplatin (four cases) and one case each of warfarin given concurrently with tamoxifen, phenytoin and cisplatin, ketoconazole with a proton pump inhibitor, phenytoin with fluorouracil, cimetidine with fluorouracil and furosemide and cisplatin. Among the 240 potential interactions between ordinary medications, the most common ones were aspirin combined with either a beta-blocker or an angiotensin-converting enzyme inhibitor (19 cases), aspirin and a corticosteroid (15 cases), warfarin and a corticosteroid (13 cases) and an angiotensin-converting enzyme inhibitor in association with prochlorperazone (nine cases). In adjusted analysis, increasing number of medications [odds ratio (OR) 1.4; \( P < 0.0001 \)], the type of medication [OR (drugs to treat comorbid conditions versus supportive care drugs) 8.6, \( P < 0.0001 \); OR (both types of medications versus supportive care drugs) 2.5, \( P = 0.018 \)] and cancer type [OR (brain versus...
Table 2. Common drug interactions identified by the studies

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Clinical event</th>
<th>Mechanism of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin + warfarin [21]</td>
<td>Deep venous thrombosis</td>
<td>Phenytoin induces warfarin hepatic metabolism with consequent reduction in its anticoagulant effect</td>
</tr>
<tr>
<td>Warfarin + omeprazole [22]</td>
<td>Upper digestive hemorrhage</td>
<td>Omeprazole inhibits hepatic metabolism of warfarin, enhancing its anticoagulant effect</td>
</tr>
<tr>
<td>Diclofenac + enoxaparin [23]</td>
<td>Postsurgical bleeding</td>
<td>Additive anticoagulant effect</td>
</tr>
<tr>
<td>Phenytion + corticosteroids [24]</td>
<td>Either seizures or phenytoin toxicity</td>
<td>Both drugs may increase or decrease each other’s liver metabolism</td>
</tr>
<tr>
<td>Warfarin + corticosteroids [25]</td>
<td>Either bleeding or thromboembolism</td>
<td>Mechanism unknown</td>
</tr>
<tr>
<td>Phenytion + acetaminophen [26]</td>
<td>Increased liver enzymes</td>
<td>Phenytion induces acetaminophen’s hepatic metabolism with consequent increased hepatic toxicity</td>
</tr>
<tr>
<td>NSAID + SSRI [27]</td>
<td>Bleeding</td>
<td>Increased risk of upper gastrointestinal bleeding; mechanism unknown, possible additive effects</td>
</tr>
<tr>
<td>Warfarin + acetaminophen [28]</td>
<td>Bleeding</td>
<td>Increased vitamin K antagonism by acetaminophen, with risk of bleeding</td>
</tr>
<tr>
<td>Benzodiazepine + omeprazole [29]</td>
<td>Somnolence</td>
<td>Inhibition of benzodiazepine’s liver metabolism, with increased sedation</td>
</tr>
<tr>
<td>Hydrochlorothiazide + cyclophosphamide/fluorouracil [35]</td>
<td>Prolonged neutropenia</td>
<td>Unknown mechanism; thiazides may prolong chemotherapy-induced neutropenia</td>
</tr>
<tr>
<td>Irinotecan + phenytoin [36]</td>
<td>Reduced efficacy of irinotecan</td>
<td>Anticonvulsants induce the hepatic metabolism of irinotecan</td>
</tr>
<tr>
<td>Warfarin + fluorouracil/capecitabine/etoposide/carboplatin/paclitaxel/gemcitabine [30–34]</td>
<td>Bleeding</td>
<td>Chemotherapy-induced protein displacement and inhibition of warfarin metabolism with a higher risk of bleeding</td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

genito-urinary tumors) 6.7, \( P = 0.0025 \) were associated with risk of drug interactions.

A similar study evaluated 100 randomly selected cancer patients >70 years and who were on active cancer-directed therapy for potential DDI [10]. The median number of medications was 9 per patient and 19% were taking cimetidine, a known CYP3 inhibitor, combined with other drugs such as carboplatin and warfarin. Curiously, no oncologist made any change in patients’ prescriptions despite being alerted about such interactions by the authors. Oncologists claimed that lack of DDI guidelines prevented them from making drug changes or adjustments.

Only one study evaluated cancer patients at the end of life. A retrospective study examined the frequency of potential DDIs among patients with advanced cancer who were receiving exclusive supportive care, i.e. they excluded patients who were receiving anticancer treatment [11]. They found that one-third (29%; 250 of 372) of patients were exposed to drug combinations with the potential to interact and that most potential drug interactions involved the same types of medications: aspirin, anticonvulsants and warfarin.

Another study in the ambulatory setting retrospectively evaluated a cohort of 135 elderly cancer patients, showing that they received a median of six medications and to whom a median of two drugs metabolized by hepatic cytochrome P-450 (CYP) enzymes were administered [12]. On regression analysis, the authors found that the use of P-450 inhibitors seemed to be associated with severe non-hematologic adverse events, although this result was not statistically significant.

real drug interactions

Two studies reported on the epidemiology of real DDIs (Table 3).

A large retrospective study analyzed all deaths that occurred in a Norwegian hospital during 2 years in order to evaluate how often deaths resulted from adverse drug reactions. They found that 18% of 732 deaths were directly or indirectly associated with adverse drug events, including drug interactions, and that 4% of the cancer-related deaths were likely to involve a severe drug-related event [13].

A retrospective study evaluated the charts of all cancer patients admitted to an oncology ward during an 8-month period for reasons of hospitalization [14]. Each hospitalization was independently evaluated by two blinded investigators using a four-point scale that was developed to classify such reasons by their probability to be associated with either a DDI or an adverse drug reaction (definitely associated, probably associated, possibly associated or unlikely associated) [14]. Among 550 hospital admissions, 458 were eligible. Among unplanned admissions (\( N = 298 \), 33 [11.0%; 95% confidence interval (CI) 7.7% to 15.2%] were associated with an adverse drug reaction and six (2.0%; 95% CI 0.7% to 4.3%) with a DDI, involving warfarin, captopril...
and anti-inflammatory agents. The most common adverse drug reaction leading to hospitalization was neutropenic fever after systemic chemotherapy. Most patients were discharged completely recovered but two patients with neutropenic fever died. Risk factors for being hospitalized to treat a DDI could not be identified due to the small number of cases of real DDIs [14].

**discussion**

Drug interactions in oncology are likely becoming common due to the exponential growth in the number of new therapeutic options of anticancer agents and their potential to prolong life expectancy of cancer patients. However, clinical consequences from DDIs have not been extensively studied in...
oncology, with many studies reporting isolated cases, small series or single-institution experiences. With only <10 studies reporting on the frequency of DDIs in oncology, it has to be determined how frequently cancer patients are exposed to real or potential DDIs.

Specifically about potential drug interactions, one-third of ambulatory cancer patients are apparently exposed to potential DDIs [9, 15]. Regardless whether patients were under chemotherapy treatment, the most dangerous combinations involve drugs to treat comorbid conditions such as antihypertensives, warfarin and anticonvulsants. Significant risk factors include presence of brain tumors/metastasis, number of medications taken by patients and use of drugs to treat comorbidities. It is likely that due to the frequent use of anticonvulsants among cancer patients with brain lesions, the tumor is a confounder as anticonvulsants, known to be enzymic inducers, are drugs known to interact with other agents [16, 17]. The number of medications is an intuitive risk factor and with respect to drugs used for comorbid illnesses, medications such as aspirin, enzyme-converting enzyme inhibitors and warfarin also have potential to interact with other drugs [18].

The available information about real drug interactions is less clear. The impact of DDIs that resulted in clinical events remains to be elucidated. However, it has been shown that real DDIs involved the same medications, warfarin, phenytoin and captopril, considered potentially hazardous by the studies that sought potential DDIs. Therefore, it is advisable to pay close attention to cancer patients taking these drugs and if feasible, safer alternatives should be prescribed; for example, LMWHs do not interact with liver CYP enzymes and could therefore substitute warfarin as an anticoagulant, considering there are no cost issues. In the case a doublet cannot be substituted, as for instance dexamethasone and phenytoin, commonly used by patients with brain lesions, patients taking these drugs should be closely monitored for adverse events and DDIs. It is of note that even though some light has been shed on the subject, the fact that they were single-institution studies and were retrospective (not carried out in real time of patient admission) might have underpowered the studies to detect clinically important DDIs. Moreover, the study patients did not have access to new molecular-targeted therapy, which makes the results less generalizable to the current practice of oncology.

The lack of studies about DDIs among cancer patients may be due to several limitations inherent to methodology involved. The major limitation of studies that screen patients' medications for potential interactions is the shortage of information about the number of such interactions that resulted in adverse clinical events. One of the main limitations is the inherent bias in evaluating real drug interactions prospectively because if a drug interaction that resulted in an adverse event has occurred, prescription adjustment and/or changes are expected to have been carried out. Obviously, it would be unethical to evaluate the clinical outcomes of drug interactions in a prospective manner without modifying or stopping the medications involved. Recall bias from patients' part and missed data from retrospective chart reviews are also important drawbacks to consider.

Studies of real drug interactions are also flawed by several confounders such as cancer signs and symptoms and the difficulty to diagnose a drug interaction and also to prove its causality. Population-based studies have the advantage of large samples and thus are less susceptible to selection bias, when compared with single-institution analyses. Another advantage is to study the prevalence of certain well-known drug interactions, for instance, by quantification of number of hospitalizations resulting from severe hemorrhage that was caused by combining warfarin with capecitabine [19]. Large population studies can even identify risk factors for drug interactions that led to hospital admission. The major disadvantage is that such studies are capable of identifying only drug interactions that led to meaningful adverse events; they cannot assess the real magnitude of drug interactions, i.e. those that led to adverse clinical events that did not bring patients to medical attention. Population studies also need representative and accurate administrative databases.

Another important aspect not covered by these studies is the economic impact of DDIs in medical oncology practice. It is important that not only serious DDIs be detected and treated, but also minor DDIs, which may make the oncologist repeat blood tests, prescribe medications to treat new symptoms and require more visits to the hospital. Population studies could address that issue in collecting information on cost incurred by hospitalizations and invasive procedures. It is recognizable, though, that the logistics of carrying out this analysis is far complex as it involves the correct diagnosis of real DDIs.

The most efficient way to prevent drug interactions when treating cancer patients has not been determined. Based on the literature, we recognize that some direct and indirect preventive approaches to detrimental drug interactions could be helpful. Among the direct initiatives, physicians could either screen all cancer patients for potentially dangerous drug combinations or focus on high-risk subjects. For the first approach, health professionals need user-friendly tools to help them screen for interactions in a quick and objective manner, given their usual busy schedule. Alert guidelines, electronic or flyers, and the development of medication databases (computerized physician order entry) linked to screening electronic programs are some examples of tools that could help health professionals to identify dangerous drug combinations. The disadvantage of screening all patients is the time spent to do it and the high likelihood to find many nonclinically significant potential drug interactions. A more logical manner is to screen patients at considerable risk for such serious drug interactions as patients taking drugs to treat concurrent illnesses, specially warfarin, anticonvulsants and antihypertensives. Other essential attitudes to prevent hazardous drug interactions include the switch of risky drugs to safer alternatives, avoid polypharmacy and be familiar with potential drug interactions involving medications that are routinely prescribed to one's patients.

Indirectly, health professionals could decrease the frequency of clinically meaningful drug interactions by increasing awareness about them. Publication of case reports, case discussion at medical rounds, teaching medical students/ residents, involving the pharmacy team to discuss patient prescription and standardized hospital monitoring of adverse drug reactions could increase the recognition and facilitate the prevention of drug interactions.
In conclusion, although it seems that one-third of cancer outpatients are at risk of DDIs, the proportion of them who actually suffer from DDIs remains unknown. Drugs that should be cautiously prescribed by physicians include warfarin, anticonvulsants and antihypertensives. There are still many issues to be investigated about the real impact of DDIs in oncology: how common DDIs involving molecular-targeted therapy are and the economic impact of DDIs on the health system. For that, large representative studies are warranted.

references