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ORIGINAL ARTICLE

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# Potential for drug interactions in hospitalized cancer patients

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**Abstract** *Objectives*: To quantify the frequency of potential drug interactions unrelated to chemotherapy in cancer patients admitted to our institution, and to define risk factors for such interactions. *Methods*: Charts of 100 consecutive hospitalized cancer patients were reviewed. Patients receiving chemotherapy and/or hormone therapy were excluded, as were patients admitted for intensive care. Drug–drug interactions were screened with Drug Interaction Facts software, and manually by the authors. Potential interactions were graded by levels of severity (severe, moderate, minor) and significance (one to five, with one representing the highest level of evidence). *Results*: The median age of the patients was 67 years, and the length of hospital stay and the number of drugs per patient were 6 days and eight drugs, respectively. In 63 patients 180 potential interactions were detected. Of the potential interactions, 18.3% were severe, 56.7% were moderate, and 25% were minor. Approximately 7%, 18% and 13% of potential interactions were graded as level 1, 2 and 3, respectively. In multivariate analysis, prescriptions with eight or more drugs ($P = 0.0004$) and six or more days of hospital stay ($P = 0.014$) were independent risk factors for potential interactions. *Conclusion*: Potential drug interactions are common among hospitalized cancer patients. Length of hospital stay and number of prescribed drugs are risk factors.

**Keywords** Drug interactions · Drug therapy · Combination · Adverse effects · Neoplasms

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## Introduction

Drug interactions are frequent in medical practice, and their incidence increases with the number of concurrent medications [5, 7, 8, 21, 23, 27, 30]. In a study among 205 outpatients seen in an emergency room in Los Angeles, the prevalence of potential drug interactions was 13% in those who received two medications, and 82% in those who were prescribed seven or more drugs [21]. The elderly are particularly prone to drug interactions, as they are more likely to take between three and seven drugs [3, 8, 22]. In addition to age, other risk factors for drug interactions are malnutrition, malabsorption, chronic liver disease (including liver metastasis), and impaired renal function [4, 12, 24, 34]. Pharmacogenetic characteristics of individual patients may also contribute to different drug effects.

Drug–drug interactions are classified into three types: pharmacokinetic, pharmacodynamic, and pharmaceutical [2, 9, 34]. Pharmacokinetic interactions occur when one drug alters the absorption, distribution, metabolism and/or excretion of another drug [2, 9, 34]. The interaction between dexamethasone and phenytoin, in which the levels of both drugs are altered, is an example of a pharmacokinetic interaction [28]. Pharmacodynamic interactions occur when there is interaction between two drugs at the same site of action [2, 9, 34]. Opioids and the selective serotonin reuptake inhibitors (SSRI) may interact in this manner [33]. When there is physical incompatibility between two different drugs, a pharmaceutical interaction may occur [6].

Cancer patients often receive multiple concurrent medications for the treatment of their tumors, comorbid conditions and cancer-related syndromes such as pain, emesis, depression, and seizures. Although the administration of multiple concurrent drugs is likely to increase the risk of undesirable drug interactions, the magnitude of this problem in oncology practice is largely unknown. In a study from Norway, in which 18% of 732 deaths that occurred in a hospital were directly or

indirectly associated with drug interactions, 4% of the patients whose death was cancer-related also had a severe drug interaction [4]. The objective of this study was to quantify the frequency and risk factors associated with potential drug interactions in cancer inpatients at our institution.

## Patients and methods

The medical charts of 100 consecutive patients with cancer who had been admitted to our oncology ward during a 6-month period were retrospectively reviewed. No patients admitted to the intensive care unit were analyzed. Patients had to be older than 18 years, and were excluded if they received chemotherapy, molecular targeted therapies and/or hormone therapy during the index hospital stay. Patients could have only one monthly admission analyzed. The medical orders for the day half-way through the hospital stay were chosen for analysis. We chose the midpoint of the hospitalization period because we believed that it would be the point at which the orders would contain the greatest number of medications. It is often the case that the number of drugs in the order decreases toward the end of the admission. Also, because the admission order is often done during the night or by the emergency room physician, at a point where the condition that leads to admission is frequently still being investigated, and the drugs in the order are still limited to those that the patient was taking at home, we reasoned that the admission order would underestimate the potential for interactions.

For each of the charts that we analyzed, all drugs in the orders were tabulated, irrespective of whether they were actually administered, and regardless of their being scheduled or on a PRN basis. Interactions were screened with Drug Interaction Facts software [13], and manually by the authors for drugs that were not recognized by the program. Potential drug interactions were graded by their level of severity (severe, moderate, minor) and scientific evidence (one to five, with one representing the highest level of literature evidence) (Tables 1 and 2) [34]. At the time the study was initiated, our hospital did not have an established automated system for detection and reporting of potential drug interactions, although, on occasion, potential interactions could be detected by one of the pharmacists and reported to the prescribing physician.

**Table 1** Drug interactions by levels of severity [34]

| Level of severity | Potential effect |
|---|---|
| 1 (severe) | An adverse effect can cause permanent damage or risk to life |
| 2 (moderate) | An adverse effect can cause harm and treatment is required |
| 3 (minor) | Small or no clinical effect, with no treatment required |

**Table 2** Drug interactions by level of evidence [34] (levels of evidence are not related to severity, prevalence, or incidence of drug interactions [34])

| Level of evidence | Type of scientific data |
|---|---|
| 1 (major) | Adverse effect confirmed by large clinical trials |
| 2 (probable) | Adverse effect with high likelihood of occurrence but without definitive randomized clinical trials |
| 3 (suspect) | Adverse effect likely to occur; data derived from case reports |
| 4 (possible) | Adverse effect may occur but data are scarce |
| 5 (unlikely) | Adverse effect may theoretically occur |

The primary objective of the study was to analyze the frequency of potential drug interactions, regardless of whether they actually occurred clinically. Other objectives were to correlate the frequency of potential drug interactions with demographic features of our patients (sex, age, type of neoplasm, presence of metastatic disease), and to identify risk factors for such interactions. We did not study potential interactions between drugs and complementary/alternative medications, herbs, or food.

Statistical calculations were done with SAS (Statistical Analysis System, Cary, N.C.). The absolute and relative frequencies of demographic and descriptive variables were tabulated for the analyses. Differences between proportions were calculated by the chi-squared test or Fisher's exact test when appropriate. Multivariate analyses were done with logistic regression models [25]. Odds ratios and their 95% confidence intervals (CI) were estimated through logistic regression models. All statistical tests were two-tailed, and $P$ values $< 0.05$ were considered significant.

**Table 3** Patient characteristics

| Variables | | Number of patients |
|---|---|---|
| Age (years) | | |
| Range | 20–94 | |
| Median | 67 | |
| Sex | | |
| Female | | 36 |
| Male | | 64 |
| Type of tumor | | |
| Solid | | 73 |
| Hematological | | 27 |
| Presence of metastasis (solid tumors) | | |
| Yes | | 66 |
| No | | 7 |
| Length of stay (days) | | |
| Range | 1–81 | |
| Median | 6 | |
| Number of drugs per patient | | |
| Range | 1–20 | |
| Median | 8 | |

## Results

Between May and October 2003, 100 consecutive eligible cancer inpatients had their charts analyzed. The main patient characteristics are shown in Table 3. The patients' ages ranged from 20 to 94 years, with a median of 67 years. Approximately one-third of the patients were women, and approximately two-thirds had metastatic solid tumors. The patients remained in hospital for 1–81 days, and for a median of 6 days. The most common causes of hospital admission were: complications of cancer treatment, such as febrile neutropenia, infections, cytopenias, severe mucositis, and chemotherapy- or radiotherapy-induced diarrhea; complications secondary to tumor progression, such as pain, spinal cord compression, thromboembolic events, bowel obstruction, neurological impairment, and terminal illness; and scheduled invasive procedures such as catheter insertion, radiofrequency ablation, hepatic arterial embolization, stereotactic radiosurgery, and drainage of cavitary effusions.

As shown in Table 3, patients received between 1 and 20 drugs, with a median of eight drugs per index medical order. Among the 100 patients analyzed, 180 potential drug interactions were found, and 63 patients (63%, 95% CI 52.8–72.4%) presented at least one potential drug interaction. Considering all the patients that were analyzed, median and mean numbers of potential drug interactions were 1 and 1.8 per patient, respectively. The levels of severity and evidence of potential drug interactions are listed in Tables 4 and 5. Of the potential drug interactions, 75% were classified as severe or moderate, and approximately 25% were major or probable regarding the level of scientific evidence.

As pointed out above, the study did not focus on the clinical consequences of drug interactions, but rather on their potential for occurrence. Nevertheless, some adverse clinical events were observed. Six patients had their levels of consciousness reduced from the combination of opioids and phenothiazines. Two patients experienced hyperkalemia with electrocardiographic changes while being treated with an angiotensin-converting enzyme inhibitor in association with spironolactone. One patient had an atrial-ventricular block due to furosemide-induced hypokalemia and the concurrent use of digoxin. Given the retrospective nature of our study, and the fact that no attempt was made to systematically collect all cases of clinically meaningful drug interactions, the above cases represent a biased estimate of the actual risk of such interactions.

A qualitative analysis was done on the drugs most commonly implicated in potential interactions. The most frequent interactions involved opioids, SSRI, benzodiazepines, phenothiazines, dexamethasone, imidazoles, thyroxine, furosemide, anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAID), low molecular weight heparins (LWMH), and omeprazole. The most frequent combinations with potential for interaction encountered were opioids with benzodiazepines, SSRI with opioids, NSAID with LMWH, dexamethasone with phenytoin, and omeprazole with benzodiazepines.

In univariate analysis (Table 6), age of 67 years or more, prescription of eight or more drugs per patient, and a hospital stay of 6 days or longer were all associated with increased odds for potential drug interactions. Sex, type of neoplasm, and presence of metastasis were not significantly associated with such interactions. In multivariate analysis, only length of hospital stay ($P = 0.017$) and number of drugs ($P = 0.0004$) were independently associated with potential drug interactions.

**Table 4** Levels of severity of 180 potential drug interactions

| Level of severity | Frequency (*n*) | 95% CI |
|---|---|---|
| Severe | 18.3% (32) | 13–24.8 |
| Moderate | 56.7% (102) | 49.1–64 |
| Minor | 25% (45) | 18.8–32 |

**Table 5** Levels of evidence of 180 potential drug interactions

| Level of evidence | Frequency (*n*) | 95% CI |
|---|---|---|
| 1 | 6.7% (12) | 3.5–11.3 |
| 2 | 17.8% (31) | 12.5–24.2 |
| 3 | 12.8% (22) | 11.3–18.5 |
| 4 | 51.7% (93) | 41.1–59.2 |
| 5 | 11.1% (19) | 6.9–16.6 |

## Discussion

The issue of chemotherapy-related drug interactions has been investigated in previous studies [15, 29]. To our knowledge, the frequency of drug interactions not related to chemotherapy has not been adequately investigated in medical oncology, as it has, for example, in internal medicine [11, 14, 17]. Given the number of clinical problems faced by patients with cancer, it is likely that drug interactions occur frequently, despite the fact that most do not have serious consequences. However, a proportion of cancer patients with drug interactions are likely to have serious complications. One hospital-based study has shown that 4% of cancer-related deaths are associated with drug interactions [4].

Inpatients are typically admitted for complications, and commonly receive more medications than when they are being treated as outpatients. The goal of the present study was to quantify the prevalence of drug interactions in the former scenario. The frequency of potential drug interactions encountered in this study (63% of patients) is of concern. The results of large studies conducted in general medicine departments are similar to ours, since approximately 67% of patients were at risk for any type

**Table 6** Univariate analysis

| Variable | Number (%) of patients | | Odds ratio (95% CI) | *P* value |
|---|---|---|---|---|
| | With interaction ($n=63$) | Without interaction ($n=37$) | | |
| Sex | | | | |
| Female | 23 (36.5) | 13 (35.1) | 1.06 (0.45–2.48) | 0.890 |
| Male | 40 (63.5) | 24(64.9) | | |
| Age (years) | | | | |
| < 67 | 24 (38.1) | 25 (67.6) | 3.38 (1.44–7.97) | 0.004 |
| ≥67 | 39 (61.9) | 12 (32.4) | | |
| Hospital stay (days) | | | | |
| < 6 | 21 (33.3) | 28 (75.7) | 6.22 (2.49–15.55) | < 0.001 |
| ≥6 | 42 (66.7) | 9 (24.3) | | |
| Type of neoplasm | | | | |
| Solid | 46 (73) | 27 (73) | 0.99 (0.39–2.49) | 0.996 |
| Hematological | 17 (26) | 10 (26) | | |
| Metastasis[a] | | | | |
| Present | 42 (91.3) | 24 (88.9) | 1.31 (0.27–6.36) | 0.705 |
| Absent | 4 (8.7) | 3 (11.1) | | |
| Number of drugs | | | | |
| < 8 | 19 (30.2) | 30 (81.1) | 9.92 (3.71–26.52) | < 0.001 |
| ≥8 | 44 (69.8) | 7 (18.9) | | |

[a]Applicable only to patients with solid neoplasms

of potential drug–drug interactions during their stay [11, 14]. It should be pointed out that our decision to analyze the midpoint of the hospital stay may have resulted in finding a higher prevalence of potential drug interactions. Had our decision been to analyze the admission orders, the discharge orders, or even all the medical orders during hospital stay, the weighted prevalence we found would likely have been lower than 63%.

The most common drugs prescribed in our study were those frequently utilized for cancer patients. Opioids, anticonvulsants, steroids, LMWH, NSAID, benzodiazepines, and antidepressants are drugs commonly used for treating complications in cancer patients. Interactions between opioids and benzodiazepines are potentially severe and have a level of evidence of four; benzodiazepines are capable of antagonizing opioid-induced analgesia [16, 31]. SSRI and tramadol coadministration is associated with the risk of serotoninergic syndrome; this interaction is classified as severe and with a level of evidence of four [33]. Coadministration of NSAID and LMWH may potentiate hemorrhagic side effects because of simultaneous inhibition of the clotting cascade and the platelet mechanisms of hemostasis [15, 35], despite the fact that a prospective study found no difference in terms of bleeding rates [35]. This drug interaction is classified as severe and with a level of evidence of four. Dexamethasone and phenytoin, frequently administered concurrently in patients with brain tumors, may constitute a severe drug interaction with a level of evidence of two; dexamethasone affects the liver metabolism of phenytoin, with a resulting increase in phenytoin serum concentrations [28]. Omeprazole and benzodiazepines may constitute a minor drug interaction with a level of evidence of three; omeprazole competitively inhibits the hepatic enzymes involved in the metabolism of benzodiazepines, thereby reducing their clearance [18].

Despite the high frequency of potential drug interactions in our study, only one-quarter of them had a solid literature background; furthermore, 11% of potential interactions found in our study were purely theoretical (Table 5). These results could be related to our screening method, given the fact that an intensified policy for detecting potential drug interactions may lead to the identification of interactions with no clinically significant meaning. The Drug Interaction Facts program [2, 20] and other software [2, 10, 11, 14, 17, 19–21, 23, 24, 26, 27, 32] have been used in other studies as screening methods for drug interactions. Most of the studies have shown good results in terms of detecting a great number of potential drug interactions [1, 10, 11, 14, 17, 19, 23, 32], although some authors do not consider the electronic method as a standard system for this purpose [20, 26]. When compared to other programs, Drug Interaction Facts is considered the most accurate, with both a sensitivity and a specificity of 97% [1].

In conclusion, the frequency of potential drug interactions not related to chemotherapy encountered in our study is of concern. These interactions seem to be more likely to occur in patients who stay longer and who receive a higher number of medications, risk factors that are more likely to be encountered among older patients with cancer. It is extremely important to recognize this increasingly common problem in medical practice, if potentially hazardous effects are to be avoided. In that sense, computerized screening programs may improve the detection and monitoring of potential drug interactions [1, 11, 14, 17, 19, 21, 23, 32]. This may in turn lead to a decreased incidence of untoward drug effects among patients with cancer. Given the results described herein,

we are currently investigating, in a prospective fashion, various aspects relating to the problem of drug interactions among our patients.

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