Original Article

Adverse Drug Reactions and Drug Interactions as Causes of Hospital Admission in Oncology

Vanessa Miranda, MD, Angelo Fede, MD, Melissa Nobuo, BS, Veronica Ayres, BS, Auro Giglio, MD, PhD, Michele Miranda, MD, and Rachel P. Riechelmann, MD, PhD

ABC School of Medicine (V.M., A.F., M.N., V.A., A.G., M.M.); and Medical Oncology Department (R.P.R.), Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Abstract

Context. Although several studies have evaluated the frequency of adverse drug reactions (ADRs) and drug-drug interactions (DDIs) in general medicine, few studies have looked at the epidemiology of adverse drug events (ADEs) in oncology.

Objectives. We sought to investigate how many hospital admissions in oncology are related to a DDI or an ADR.

Methods. All cancer patients admitted to an oncology ward during an eight-month period had their charts retrospectively evaluated for reasons of hospitalization, using a 4-point scale (definitely, probably, possibly, or unlikely associated) to classify admissions by their probability of being associated with either a DDI or an ADR.

Results. From September 2007 to May 2008, there were 550 hospital admissions and 458 were eligible. Among unplanned admissions (n = 298), 39 (13.0%, 95% confidence interval [CI] 9.4%–17.4%) were considered to be associated with an ADE, 33 (11.0%, 95% CI 7.7%–15.2%) with an ADR, and six (2.0%, 95% CI 0.7%–4.3%) with a DDI. The most common DDIs involved warfarin, captopril, and anti-inflammatory agents, and the most frequent ADR was neutropenic fever post-chemotherapy. Most patients were discharged completely recovered, but two patients died.

Conclusion. Approximately one in 10 unplanned hospitalizations of cancer patients is associated with an ADE. Prospective and population-based studies are warranted to evaluate their magnitude in oncology. J Pain Symptom Manage 2011;42:342–353. © 2011 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Supportive care, toxicity, adverse drug reactions, oncology, drug interactions

Address correspondence to: Rachel P. Riechelmann, MD, PhD, Medical Oncology Department, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Arnaldo 251, 5th Floor, São Paulo, SP, 01246-000, Brazil. E-mail: rachelri2005@gmail.com

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Introduction

Adverse drug events (ADEs) relate to any clinical or laboratory alteration incurred by a patient that is directly or indirectly associated with an administered medication. An ADE can be either a drug-induced side effect (or adverse drug reaction [ADR]) or a drug-drug, drug-food, or drug-herb interaction. The World Health Organization defines an ADR as “... one that is noxious, unintended, and occurs at doses normally used in man.”

With respect to drug-drug interactions (DDIs), pharmacology texts define them as instances in which a medication interferes with the pharmacokinetic, pharmacodynamic, or pharmaceutical properties of another drug, resulting in an altered net effect of one or both drugs.

ADEs are a major concern in health care. Although several studies have evaluated the frequency of ADRs and DDIs in general medicine, few studies have looked at the epidemiology of ADEs in oncology. Because cancer patients receive numerous medications, they are at particular risk for an ADE, such as a DDI. Studies of ambulatory cancer patients have shown that approximately one-third of them were at risk for DDIs, with most involving medications to treat comorbidities, such as anticoagulants and antihypertensives. A retrospective evaluation of 100 hospitalized cancer patients found that two-thirds had been prescribed one or more drug combinations with the potential to interact during hospitalization.

Several studies have analyzed ADRs for patients with general medical conditions. A recent systematic review showed that approximately 5%–6% of patients with different medical conditions present with an ADR as a contributing factor to hospital admission. Information on frequency of ADRs as a cause of hospitalization in oncology is scarce. An evaluation of causes of death in a Norwegian hospital identified 18% of more than 700 deaths to be associated with an ADE and 4% of all cancer-related deaths were likely to be associated with a serious interaction.

Given the lack of information on the epidemiology of ADEs in oncology, we sought to assess how many hospital admissions in oncology are associated with a DDI or an ADR.

Patients and Methods

Study Design

This was a retrospective cohort study of all consecutive cancer patients admitted to the oncology ward of a teaching hospital (Mario Covas) located in the greater Sao Paulo area in Brazil, during an eight-month period. The hospital is a 300-bed public and teaching institution that serves more than three million people. The local ethics board reviewed and approved the study.

We reviewed the medical records of consecutive adult cancer patients admitted at our institution to identify hospital admissions that were possibly associated with an ADE. Patients receiving treatment within a clinical trial were excluded. ADEs involving food-related interactions, multivitamins, and herbs were not considered.

Each hospital admission was evaluated by two independent and blinded investigators who evaluated the cause(s) of admission and classified it by its probability of being associated with either a DDI or an ADR. After classifying the admission, the investigators thoroughly reviewed the medical records to gather information about patient demographics, tumor characteristics, and type of treatment received within four weeks of admission, comorbid illness(es), and medications used before hospitalization. A comorbid condition was defined as a clinical situation that required pharmacological intervention, and its severity was graded using the Charlson Comorbidity Index. The Charlson Comorbidity Index was initially developed to score the risk of death among hospitalized noncancer patients. Although it has not been validated in the oncology population, we considered it acceptable to use as a measure of comorbidity severity in this study. The number of medications for each subject was calculated by summing all pharmacological compounds, and each one was considered an individual medication for analysis, regardless of drug schedule; for example, commercial combinations of oxycodone/acetaminophen were counted as two drugs, oxycodone and acetaminophen, and short- and sustained-release morphine was counted as one drug. Multivitamins, as described above, were not considered.

For admissions suspected to involve an ADE, additional information was gathered on patient
outcomes (stable outcome: when the patient was kept on the ward and had no life-threatening complications; unstable outcome: when the patient was transferred to an intensive care unit and/or had life-threatening complications; or fatal outcome), clinical status at discharge (completely recovered, partially recovered, or death), need for invasive procedure to treat ADE complications, and need of specialist consultation.

Classification of Reasons for Hospital Admission

Causes of admission were examined independently by two blinded investigators (MCM, MNF), using a 4-point scale (Table 1) developed by the authors. They agreed on all but seven classifications, when a third investigator (RPR) was consulted, and consensus was achieved. The scale was adapted from the World Health Organization causality criteria (probable, possible, and unlikely) and pilot ed in the first 30 hospital admissions. After minor fine-tuning, the scale classified admissions into four different categories: definitely associated with an ADE, probably associated with an ADE, possibly associated with an ADE, or unlikely associated with an ADE.

The classification of causes of hospital admission was based on medical record review and discussion with medical oncologists. To classify each admission, the authors reviewed the complete medical history that led to hospitalization, including the medications used by patients immediately before and at the time of admission, symptomatology, tumor type and stage, and oncology treatment. In addition, patient medication lists at the time of admission were entered into the Drug Interaction Facts software version 4.0 (available from www.factsandcomparisons.com, Lippincott Williams & Wilkins, St. Louis, MO), which contains a comprehensive database of drug monographs and DDI lists, and which has been used in other studies. Subsequently, the information about drugs was put in the context of medical history at admission and discussed among the authors, followed by discussion with medical oncologists. When obvious drug-unrelated causes of admission were identified, the admission was regarded as unlikely associated. Examples of such admissions include the following: disease progression, admissions to treat patients with continuous infusion chemotherapy, or elective colostomy reversal. The authors agreed on all classifications except for one case for which the admission was considered as a drug interaction-related hospitalization, but the actual drug interaction occurred during hospitalization and not as the primary cause of admission. The patient was admitted for breast cancer surgery and developed postoperative hemorrhage secondary to a drug interaction between enoxaparin and aspirin. Details are presented in Table 4.

After the initial classification, the investigators evaluated the cause of each admission in an attempt to enhance the internal validity of this study, that is, to focus on the admissions that were not elective hospitalizations and do

<table>
<thead>
<tr>
<th>Type of Hospital Admission</th>
<th>Probability of an ADE Being Associated with Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Definitely associated. ADE was the sole cause of hospital admission.</td>
</tr>
<tr>
<td>2</td>
<td>Probably associated. ADE significantly contributed to hospital admission.</td>
</tr>
<tr>
<td>3</td>
<td>Possibly associated. ADE somewhat contributed to hospital admission.</td>
</tr>
<tr>
<td>4</td>
<td>Unlikely associated.</td>
</tr>
</tbody>
</table>

*An ADE includes both ADR and DDI.
not reflect the scenario of admissions secondary to cancer-related complications. The admissions were then considered either planned (elective scheduled interventions, such as port insertion, continuous infusion chemotherapy, and elective biopsies) or unplanned (when it was an urgent situation, mostly clinical complications from cancer or its treatment). The focus of this study was the unplanned hospital admissions (UHAs).

Statistical Considerations

Two previous studies with nearly 400 patients found a 30% frequency of potential DDIs with a 10% variance for the 95% confidence interval (CI). Based on these results, we determined that 400 hospital admissions would be sufficient to evaluate how many admissions were caused by ADEs among cancer patients. We used summary statistics to describe patient characteristics and frequency and types of hospital admissions associated with an ADE, separately for ADRs and DDIs. The unit of analysis was hospital admission; therefore, the same patient could be included more than once. Logistic regression was used to identify factors associated with being hospitalized for an ADR (admission definitely, probably, or possibly associated with an ADE vs. unlikely), considering planned hospital admissions and UHAs. The small number of admissions associated with a DDI prevented any exploratory analysis. Independent variables tested included the following: age (median age: 57 years, <57 years, or ≥57 years), cancer type (solid or hematological), severity of comorbid conditions (median Charlson Comorbidity Index: 2, score <2, or ≥2), receipt of chemotherapy within four weeks of hospital admission (yes or no), and number of medications taken by patients at hospital admission (median number of drugs taken by patient: 3, <3, or ≥3). For binary variables, the group at lower risk of the outcome was chosen as the referent. Variables with univariate P-values <0.1 were entered into the multivariable model. In the multivariable model, predictors were considered statistically significant if the P-value was <0.05. The Statistical Package for the Social Sciences version 13 (SPSS, Inc., Chicago, IL) was used for all analyses.

Results

From September 2007 to April 2008, there were 550 admissions and 458 were eligible; 92 were excluded because they were participating in clinical trials. Many patients were admitted more than once during the study period: 39 patients were admitted twice, and 41 were admitted more than twice. Table 2 summarizes patient characteristics considering only one admission (the first admission) per patient (n = 294). The median age was 58 (range 15–91), more than half were male, the most common tumor type was gastrointestinal, and the median number of drugs per patient was two (range 1–8).

Among all 458 hospital admissions, 160 were planned and 298 were UHA. The most frequent reasons for planned hospitalization were scheduled intravenous chemotherapy administered by continuous infusion (36%), surgical intervention (12%), and diagnostic workup (9%). The most common causes of UHA were clinical deterioration requiring supportive care and/or pain control (30%). Considering only UHA, 39 admissions (13.0%, 95% CI 9.4%–17.4%) were considered to be consequent to an ADE: six because of a DDI (2.0%, 95% CI 0.7%–4.3%) and 33 (11.0%, 95% CI 7.7%–15.2%) because of an ADR (Table 3). The DDIs involved warfarin,
<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Probability of an ADE to be Associated with Hospitalization</th>
<th>Medical History at Admission</th>
<th>Cause of Admission</th>
<th>Mechanism</th>
<th>Length of Admission (Days)/Evolution/Clinical Status at Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril + hydrochlorothiazide (Clarke et al., 1991)</td>
<td>Probably associated.</td>
<td>54-year-old female with advanced bladder cancer on exclusive supportive care, type II diabetes, and high blood pressure treated with hydrochlorothiazide presented with asthenia and symptoms of arterial hypotension after starting captopril. Captopril was stopped and blood pressure normalized. The additive effect of the two antihypertensive agents coupled with the frail clinical condition of the patient may have led to hospital admission.</td>
<td>Arterial hypotension</td>
<td>Additive hypotensive effects.</td>
<td>Seven/stable/completely recovered.</td>
</tr>
<tr>
<td>Captopril + dexamethasone</td>
<td>Probably associated.</td>
<td>80-year-old male with non-Hodgkin's lymphoma, receiving supportive care exclusively, had chronic renal failure and arterial hypertension controlled with captopril and hydrochlorothiazide for the past four months, presented with high blood pressure after started on high-dose dexamethasone. Blood pressure decreased after the patient was given antihypertensive agents.</td>
<td>Arterial hypertension</td>
<td>Dexamethasone induces sodium retention, which antagonizes hypotensive effects of captopril.</td>
<td>12/stable/completely recovered.</td>
</tr>
</tbody>
</table>
was admitted for upper digestive hemorrhage and INR = 6. The dose of omeprazole was increased to 40 mg/day po a few days before admission. Warfarin was discontinued until INR was 3, and a low molecular weight heparin was started.

<table>
<thead>
<tr>
<th>Aspirin + enoxaparin (Macie et al., 2004)</th>
<th>Definitely associated.</th>
<th>Post-surgical bleeding and melena</th>
<th>Hemorrhage from the combination of an anticoagulant and an antiaggregation agent</th>
<th>Seven to 18 days/short-term unstable/completely recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>63-year-old female with localized breast cancer, arterial hypertension controlled with captopril and hydrochlorothiazide, had recent breast surgery and was started on prophylactic low molecular weight heparin. Presented with surgical scar bleeding after restarted on aspirin.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72-year-old male with extensive small-cell lung cancer, not on chemotherapy, known history of arterial hypertension and who was taking long-term aspirin and omeprazole, presented with melena a few days after starting dexamethasone for bone pain. He was admitted, and a gastric bleeding ulcer was diagnosed by upper endoscopy. Red blood cell transfusion was required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INR = international normalized ratio.

*The interaction between captopril and dexamethasone is considered theoretical, with no clinical case reported in the literature. We considered it clinically significant because the patient had arterial blood pressure under control before admission.
captopril, and anti-inflammatory agents and anticonvulsants (Table 4). The most frequent ADRs were neutropenic fever (20 instances) caused by cytotoxic chemotherapy (Table 5).

Most patients admitted for an ADE were clinically stable ($n = 33/39, 84.6\%$) and recovered completely by the time of discharge ($n = 34, 87.2\%$). Two of 20 patients who were admitted for febrile neutropenia died of sepsis (mortality rate $= 10\%, 95\%$ CI $= 1.2\%–31.6\%$). A 60-year-old male with advanced non-small cell lung cancer who had received carboplatin and paclitaxel two weeks before admission was admitted to treat febrile neutropenia; he developed hemodynamic instability and died on the ward after three days. The other patient was a 32-year-old female with localized breast cancer who was being treated with adjuvant cyclophosphamide, methotrexate, and leucovorin. She was admitted because of febrile neutropenia and hemodynamic instability. She died after 14 days. Both patients received standard care with broad-spectrum antibiotics, blood transfusion, and granulocyte-colony stimulating factors (G-CSF).

Univariable analysis ($n = 458$) identified the number of medications taken by patients, receipt of systemic chemotherapy within four weeks of admission, and cancer type as risk factors for patients to be hospitalized for an ADR (Table 6). In adjusted analysis, cancer type and receipt of chemotherapy remained significant. Patients with hematologic malignancies were 12 times more likely to be admitted for an ADR than were those with solid tumors (odds ratio [OR]: 12.1, 95% CI 5.9–25.0; $P < 0.0001$). Patients who received chemotherapy within four weeks before hospitalization had a tenfold risk of being admitted for an ADR than were those who did not receive chemotherapy within this time frame (OR: 10.8, 95% CI 5.3–22.1; $P < 0.0001$).

**Discussion**

The present study showed that one in 10 cancer patients was hospitalized to treat an ADR. Although febrile neutropenia was obviously common, other ADEs, including DDIs and ADRs, also were identified. Although most patients recovered and were discharged from hospital in good clinical condition, two patients admitted for febrile neutropenia died despite receiving standard treatment.

We are unaware of studies on the frequency of ADEs as causes of hospitalization in oncology. A recent systematic review of 25 studies in general medicine conducted over the last 19 years demonstrated that approximately 6% of adult patients and 11% of the elderly were admitted to treat complications from ADRs, with the drugs most commonly involved being cardiovascular medications, nonsteroidal anti-inflammatory drugs (NSAIDs), and central nervous system drugs. A Dutch retrospective cohort of more than 3500 patients with different illnesses also found a similar prevalence of hospitalization for ADRs (5%), and in 0.3% of patients, the outcome was fatal. In that study, neutropenic fever was among the most common causes of admission.

Because cancer patients often receive chemotherapy with a substantial risk of side effects, their chance of being hospitalized for ADEs is expected to be higher than that for patients without cancer. Moreover, drug pharmacokinetics may be altered in cancer patients because of malnourishment, organ dysfunction, and edema. Indeed, we found that 12.7% of hospital admissions were associated with an ADE, roughly triple the 5% rate reported for adult noncancer patients. This is likely caused by cytotoxic chemotherapy, which is known to be highly toxic. Our multivariable analysis showed that cancer patients who received chemotherapy close to admission were at risk of being hospitalized for an ADR in comparison with those who did not. Similar to the Dutch cohort, we identified febrile neutropenia as a common ADR leading to hospitalization.

Presence of hematological malignancies was a risk factor for an ADR-associated hospitalization. Febrile neutropenia was responsible for hospital admission for one in 29 U.S. cancer patients receiving cytotoxic chemotherapy from 1999 to 2005 and for one death for every 14 hospitalized patients. The mortality rate of febrile neutropenia among our patients was 10%, which does not differ significantly from that reported for the U.S. patients, despite probable differences in socioeconomic status. The U.S. study also found that hospitalization for neutropenia was more common in patients with a
### Table 5
**Description of Hospital Admissions Associated with ADR**

<table>
<thead>
<tr>
<th>ADR</th>
<th>Number of Instances</th>
<th>Probability of an ADE to be Associated with Hospitalization</th>
<th>Medical History at Admission</th>
<th>Length of Admissions (Days)/Evolution/ Clinical Status at Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia post systemic chemotherapy</td>
<td>20</td>
<td>Definitely associated.</td>
<td>Patients with various tumor types (nine had hematological cancers) presented with fever and neutropenia seven to 20 days after receipt of cytotoxic chemotherapy. Patients did not receive prophylactic colony stimulating factors but all received it while in hospital to treat febrile neutropenia.</td>
<td>Median of seven days (range 2–14)/17 patients had a stable clinical course, one patient was taken to the intensive care unit; all 18 were discharged completely recovered. Two patients died in hospital.</td>
</tr>
<tr>
<td>Mucositis after systemic chemotherapy</td>
<td>6</td>
<td>Definitely associated.</td>
<td>Four patients with non-Hodgkin’s lymphomas and two with gastric cancer developed oral and/or intestinal mucositis after receiving chemotherapy (methotrexate or fluoropyrimidines). Patients received local oral mouthwash, painkillers, hydration, and sometimes, antibiotics.</td>
<td>Median of seven days (range 5–8)/all patients except one had a stable clinical course and were discharged completely recovered. One patient had hemodynamic instability because of dehydration but recovered later after IV fluids.</td>
</tr>
<tr>
<td>Chemotherapy-induced nausea and vomiting</td>
<td>1</td>
<td>Definitely associated.</td>
<td>34-year-old male with colorectal cancer treated with Folfox regimen. He took steroids for chemotherapy-induced nausea and vomiting prophylaxis, but four days after treatment, he developed severe nausea and vomiting and was admitted to receive IV fluids and IV antiemetics.</td>
<td>10 days/stable clinical course/completely recovered.</td>
</tr>
<tr>
<td>Constipation and abdominal pain</td>
<td>3</td>
<td>Definitely associated.</td>
<td>Two patients (36 and 56 years old) with advanced colorectal cancer were treated with Folfox and a 70-year-old male also with colorectal cancer not receiving chemotherapy but tramadol 40 mg/daily po developed severe constipation and abdominal pain. They were treated with stool softeners, laxatives, fluids, nonopioid analgesics; the dose of tramadol was decreased to 300 mg/day po, and stool softeners were given prophylactically.</td>
<td>Seven to 15 days/stable clinical course/discharged in good clinical condition.</td>
</tr>
<tr>
<td>ATRA syndrome</td>
<td>1</td>
<td>Definitely associated.</td>
<td>75-year-old male with acute promyelocytic leukemia who was receiving ATRA developed ATRA syndrome with dyspnea, prolonged fever, and asthenia. He was admitted and treated with dexamethasone.</td>
<td>Spent seven days in hospital/stable clinical course/discharged completely recovered.</td>
</tr>
<tr>
<td>Arterial hypertension and seizures</td>
<td>1</td>
<td>Definitely associated.</td>
<td>63-year-old male with advanced non-small cell lung cancer, with no evidence of brain metastasis and no known comorbid conditions started treatment with platin-based chemotherapy combined with bevacizumab. After one month, the patient was admitted with hypertensive crisis and seizures. He received</td>
<td>Spent four days in hospital/good clinical course but was discharged with high blood pressure.</td>
</tr>
</tbody>
</table>

(Continued)
hematological malignancy than for those with solid tumors. These findings reflect the intense anticancer regimens coupled with the underlying aggressive nature of these diseases.

Cancer patients usually receive many medications to treat comorbid illness and/or as supportive care. Two studies by Riechelmann et al. showed that each additional drug taken by patients increases the risk of DDIs, although the number of medications taken by patients was not a significant risk factor for an ADR in the adjusted analysis. It is possible that type of drug is more important than the number of medications in predisposing patients to experience ADRs.

The proportion of DDIs leading to hospital admission of cancer patients is unknown. Among our patients, six patients were hospitalized to treat the clinical consequences of DDIs, such as thromboembolism resulting from phenytoin-induced reduction in hepatic metabolism of warfarin and hemorrhage from the additive effects of NSAIDs and low molecular weight heparin. Studies of potential DDIs showed that one-third of ambulatory Canadian cancer patients take drug doublets with the potential to interact, mostly not involving chemotherapy but medications to treat comorbid illnesses, such as warfarin, captopril, and phenytoin, the same drugs associated with hospitalization for a DDI in the present analysis. Screening of cancer patients’ medications to identify those taking these agents could identify potentially dangerous drug combinations and avoid hazardous clinical outcomes.

Our study has limitations. The study population came from a single institution, and although it is representative of the general cancer patients seen in the public setting, selection bias was possible. Brazil is a developing country, with heterogeneous access to health care, such that 80% of the population, ours included, does not have access to expensive cancer treatments, including most molecular targeted agents. Molecular targeted agents are being prescribed increasingly in cancer treatment, and although their side effects are different from those of cytotoxic chemotherapy, they may lead to serious adverse events. Clinically significant cardiotoxicity has been reported in up to 15% of patients treated with sunitinib, an agent that targets...
tyrosine kinase receptors, including the vascular endothelial growth factor receptor,\textsuperscript{16} and about 4\% of breast cancer patients treated with trastuzumab, a HER2/neu-target monoclonal antibody, develop symptomatic cardiac dysfunction.\textsuperscript{17} Although we identified a patient who developed severe high blood pressure after receiving bevacizumab, the prevalence of hospitalizations associated with ADEs from molecular targeted cancer agents could not be evaluated. Another limitation was the lack of involvement from a clinical pharmacist, which might have hampered the identification of ADRs and DDIs.

There is no established method to identify clinically significant ADEs, and chart reviews and/or patient interviews have been used often; we identified ADEs by medical record review. Also, although it has been estimated that 60\%–70\% of ADEs reported in general medicine and about 20\% of hospital admissions of cancer patients for ADEs are preventable,\textsuperscript{18,19} we did not evaluate preventability of ADEs. This is because criteria used to define an ADE as avoidable include patient compliance and a detailed medical history\textsuperscript{20} (such as allergy history), which could not be captured reliably in a retrospective study. Here, we focused on ADEs that resulted in hospitalization, although we recognize the potentially large number of minor ADEs misdiagnosed because of cancer symptomatology and comorbidities.

Cost analysis was not performed, but the cost of morbidity and mortality associated with hospitalizations for ADEs is substantial. A U.S. study showed that the mean cost of hospitalization to treat febrile neutropenia was $13,372 per admission.\textsuperscript{21}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.7 (0.4–1.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Number of medications taken by patient at admission</td>
<td>3.3 (1.7–6.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Receipt of chemotherapy</td>
<td>12.2 (6.1–24.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Type of cancer (hematologic vs. solid tumor)</td>
<td>4.4 (2.3–8.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Severity of comorbid illness (Charlson Comorbidity Index $\geq$2)</td>
<td>1.2 (0.5–3.0)</td>
<td>0.632</td>
</tr>
</tbody>
</table>

Cancer brings great physical and psychological burdens to patients and their caregivers. Ways to minimize patient suffering include the avoidance of futile interventions, such as unnecessary prescriptions. Prevention of ADEs in cancer patients requires increasing awareness of the pharmacology of agents commonly prescribed. Because many DDIs found here were the same ones found in a study of potential DDIs, screening tools, such as flyers listing the most dangerous combinations, or electronic programs, could help to identify risky doublets and prevent their consequences. Avoidance of polypharmacy and medication reconciliation also can help to decrease the risk of an ADE. Improved patient reporting of ADEs is also pivotal. Studies that compare patient self-reporting with physician capturing ADEs have shown that patients do not always express their concerns about ADEs unless their doctors inquire about them.\textsuperscript{22} Use of electronic patient self-report tools to identify possible ADEs seems useful,\textsuperscript{23} although not applicable to many patients (illiterate and functionally impaired individuals); strengthening patient–doctor relationships may help cancer patients to better report their symptoms. Cultural background also plays a role in determining how often patients report their symptoms.

Despite the strategies described above to reduce clinically significant ADEs, it is impossible to avoid all cancer therapy-induced ADEs. There must be a balance between an “acceptable” rate of ADEs and dose-intensity of anticancer agents. For chemotherapy regimens from which a 20\% rate of febrile neutropenia is anticipated, oncology guidelines advise on the use of prophylactic G-CSF, when the cost of such agents is not an issue.\textsuperscript{24} In our setting, dose reductions and cycle delays of anticancer agents are used as an alternative to prophylactic G-CSF because of reimbursement issues, although they may compromise drug efficacy, especially in the adjuvant setting. Therefore, the acceptable tradeoff between the risks of...
a serious ADE vs. the dose-intensity delivered has not yet been established. Recognizing this limitation, we suggest more attention be paid to patients with hematological malignancies and those receiving anticancer therapy. A hospitalization for an ADE may decrease treatment efficacy because of treatment interruption, lead to life-threatening complications and/or long term disability, and ultimately have a fatal outcome.

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