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Potential drug interactions and chemotoxicity in older patients with cancer receiving chemotherapy

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ABSTRACT

Purpose: Increased risk of drug interactions due to polypharmacy and aging-related changes in physiology among older patients with cancer is further augmented during chemotherapy. No previous studies examined potential drug interactions (PDIs) from polypharmacy and their association with chemotherapy tolerance in older patients with cancer.

Methods: This study is a retrospective medical chart review of 244 patients aged 70+ years who received chemotherapy for solid or hematological malignancies. PDI among all drugs, supplements, and herbals taken with the first chemotherapy cycle were screened for using the Drug Interaction Facts software, which classifies PDIs into five levels of clinical significance with level 1 being the highest. Descriptive and correlative statistics were used to describe rates of PDI. The association between PDI and severe chemotoxicity was tested with logistic regressions adjusted for baseline covariates.

Results: A total of 769 PDIs were identified in 75.4% patients. Of the 82 level 1 PDIs identified among these, 32 PDIs involved chemotherapeutics. A large proportion of the identified PDIs were of minor clinical significance. The risk of severe non-hematological toxicity almost doubled with each level 1 PDI (OR = 1.94, 95% CI: 1.22-3.09), and tripled with each level 1 PDI involving chemotherapeutics (OR = 3.08, 95% CI: 1.33-7.12). No association between PDI and hematological toxicity was found.

Conclusions: In this convenience sample of older patients with cancer receiving chemotherapy we found notable rates of PDI and a substantial adjusted impact of PDI on risk of non-hematological toxicity. These findings warrant further research to optimize chemotherapy outcomes.

1. Introduction

Increasing age and polypharmacy are associated for a number of reasons. These include: increased prevalence of multimorbidity;[1–6] absence of a primary care provider able to coordinate the care of different specialists;[7,8] and increased use of alternative forms of treatments.[9] Also older individuals may keep taking medications they no longer need when multiple physicians and multiple sites of care are involved.[8]

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Information related to polypharmacy in older patients with cancer is limited.[10] Six studies[5,11–15] were conducted in ambulatory and three[16–18] in hospitalized patients with cancer. All studies revealed high prevalence of polypharmacy, and its associated risk of drug interactions. The risk of interaction ranged from 29 to 58%,[13,15,16] and in two studies[16,17] the risk of inappropriate prescriptions varied between 29 and 41%. None of the studies assessed the clinical consequences of polypharmacy. In our program, older patients take an average of 6 medications, 2 of them being metabolized by p450, a key player (although not the only one) in drug interactions.[19]

In the present study we investigated the prevalence and severity of drug–drug interactions in older patients with cancer receiving chemotherapy, the association between drug interactions and chemotherapy-related toxicity, and the correlation between the risk of drug-drug interactions and the number of medications taken by each patient. The Senior Adult Oncology Program (SAOP) at the Moffitt Cancer Center in Tampa represents a suitable setting for this research. Established in 1993 for the management of patients with cancer aged 70 and over, the SAOP collects comprehensive baseline information, including a geriatric screening and a record of all medications the patients take at initial presentation, using self reports, brown bag approach, and previous medical records. It updates the medication list at each subsequent visit.

2. Methods

2.1. Study Design and Participants

This is a retrospective medical record review of patients with cancer aged ≥70 years who received chemotherapy in the SAOP in 1995–2005. This study was approved by the Institutional Review Board at the University of South Florida. It uses a cohort that we created to study the impact of p450 interactions on tolerance of chemotherapy in the elderly.[19] We reviewed the records of all patients who received regimens including at least one chemotherapeutic agent metabolized by the cytochrome p450 (CYP) enzymatic complex (N = 371), as identified through the Moffitt chemotherapy pharmacy administration records. Patients with incomplete data were excluded from the analyses, which rendered a final sample size of 244 patients.

We extracted data from medical records on all the drugs (i.e. chemotherapy and non-chemotherapy prescription drugs, over the counter drugs [OTC], herbals, and supplements) taken with the first chemotherapy cycle. Nurses at Moffitt are required to fill out a comprehensive medication profile for each patient at each visit. This medication profile is available in both the hard copy and the electronic medical records. We screened for drug interactions among all the drugs extracted using the Drug Interactions Facts™ software.[20] This software is based on current published data and showed superior accuracy, comprehensiveness, sensitivity, and specificity in a study comparing it to other PDA-compatible drug interaction resources, which makes it an interesting candidate for use in daily clinical practice.[21] It has been used in several oncology drug interaction studies.[14–16,22] Drug Interaction Facts™ classifies PDIs into five levels of clinical significance based on timing of onset (i.e. rapid, delayed), level of severity (i.e. major, moderate, minor), and level of supportive documentation (i.e. established, probable, suspected, possible, unlikely) (Table 1).

We extracted the recorded chemotherapy adverse events (AE) which occurred over the entire duration of the chemotherapy, and rated their severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf]. Patients were assigned a value of 1 for the non-hematological toxicity variable if they experienced any grades 3–4 non-hematological AE; otherwise patients were assigned a value of 0. Similar coding was implemented if patients experienced any of the grade 4 hematological AE (hematological toxicity variable = 1). Because previous studies showed that the characteristics of the patient, the malignancy, and the chemotherapy regimen received are correlated with the risk of chemotherapy-related toxicity, we extracted these data as well and adjusted for these factors when assessing the relationship between PDI and chemotherapy complications.[23–27] These factors included: pretreatment clinical characteristics including demographics (age, gender), body mass index (BMI), blood pressure, Eastern Cooperative Oncology Group performance status (ECOG-PS), and malignancy stage; pretreatment laboratory values including red blood cell count (RBC), plasma albumin, total bilirubin, aspartate aminotransferase (AST), and creatinine clearance; and the intrinsic toxicity of each chemotherapy regimen using the MAX2 index developed by Extermann et al.[23,28] Our database did not include comorbidity data. As our work and that of others shows no or inconsistent impact of comorbidity on chemotherapy toxicity (see Discussion for more details), we considered this limitation as acceptable.[23,29–33]

2.2. Statistical Analyses

Descriptive summary statistics were used to illustrate the sample characteristics, the rates of PDI, and the chemotherapeutics commonly involved in PDI. Pearson correlations were

Table 1 – Definition of level of significance of potential drug interactions according to Drug Interaction Facts.[20]

Level of significance	Definition
1	Potentially severe or life-threatening interaction; occurrence has been suspected, established, or probable in well controlled studies.
2	Interaction may cause deterioration in patients' clinical status; occurrence suspected, established, or probable in well controlled studies.
3	Interaction causes minor effects; occurrence suspected, established, or probable in well controlled studies.
4	Interaction may cause moderate-to-major effects; data are limited.
5	Interaction may cause moderate-to-major effects; occurrence is unlikely or there is not good evidence of an altered clinical effect.