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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 (PDI) 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 Interactions 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 PDI 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

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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.

Keywords

Chemotherapy; drug interactions; geriatric oncology; elderly; chemotoxicity; CTCAE; Drug Interaction Facts[™]; drug interaction software

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).

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.

METHODS

Study Design and Participants

This is a retrospective medical record review of patients with cancer aged 70 years and older 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 to 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 interactions resources, which makes it an interesting candidate for use in daily clinical practice (21). It has been used in several oncology drug interaction studies (e.g. (14–16, 22). Drug Interactions 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 National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_v3.pdf]. Patients were assigned a value of 1 for the non-hematological toxicity variable if they experienced any grade 3–4 non-hematological AE; otherwise patients were assigned a value of 0. Similar coding was implemented if patients experienced any 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: (1) pretreatment clinical characteristics including demographics (age, gender), body mass index (BMI), blood pressure, Eastern Cooperative Oncology Group performance status (ECOG-PS), and malignancy stage; (2) pretreatment laboratory values including red blood cell count (RBC), plasma albumin, total bilirubin, aspartate aminotransferase (AST), and creatinine clearance; and (3) 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).

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 used to examine binary relationships between the number of PDI and total number of drugs taken per patient. Logistic regression models were used to examine the association between PDI and risk of severe hematological and non-hematological toxicity during chemotherapy. All logistic regressions were adjusted for the patients' clinical, laboratory, and chemotherapy regimen characteristics described above. Separate models were examined for the following dependent variables: Total number of PDI of all levels; total number of PDI with the highest level of clinical significance (level 1, level 2, and level 1–3 respectively); total number of PDI of all levels involving chemotherapy drugs; and total number of PDI involving chemotherapy drugs with the highest level of significance (defined as above). We examined only the impact of the highest levels (e.g., levels 1–3) of PDI to parallel previous researchers' ascertainment of their clinical significance (14). Level of statistical significance was set at the conventional $P < 0.05$. Analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Epidemiology

The sample characteristics are presented in Table 2. Sixty-six patients (27%) experienced a G4 hematological toxicity; 126 patients (51.6%) experienced a grade 3–4 non-hematological toxicity; among them, 40 (16.4%) experienced both types of toxicity.

At the time of chemotherapy initiation, patients in our sample reported taking a mean of 11.7 ± 4.6 drugs (range 3–41), including prescription chemotherapy and non-chemotherapy drugs, over the counter drugs, herbals, and supplements. We identified 769 PDIs affecting 184 (75.4%) patients. The distribution of the identified PDI is presented in Table 3. A large proportion of the identified PDI had minor clinical significance (i.e., levels 4–5). As expected, the total number of drugs taken was highly correlated with the total number of PDI ($r = 0.61$, $P < 0.001$).

There were 225 PDI identified involving chemotherapeutics. Out of these 32 were level 1 affecting 14.2% of patients, 25 were level 2 among 6.6% of patients, and none was level 3. About three quarters of these PDI were of minor clinical significance (e.g., levels 4–5). Table 4 describes the PDI involving chemotherapeutics with the highest levels of significance and their potential outcomes. None of the PDI involving chemotherapeutics included interactions with herbals or supplements.

The risk of PDI per patient increased with the number of medications and was almost 100% in patients taking 8 or more drugs. Although 49.3% (total level 4 + level 5 = 379/769) of the total PDIs detected were of minor clinical significance, 21.3% of patients had at least one level 1 PDI and 14.2% of patients had at least one level 1 PDI involving chemotherapeutics.

PDI and Toxicity

There was a strong correlation between total number of drugs and total number of PDI per patient but no association between total number of PDI and complications of chemotherapy. In the adjusted models none of the PDI indicators were significantly associated with the risk of severe hematological toxicity. However, the adjusted risk of non-hematological toxicity increased by 17% (OR= 1.17, 95% CI: 1.01–1.35) for each additional level 1–3 PDI, by 94% (OR= 1.94, 95% CI: 1.22–3.09) for each additional level 1 PDI; by 29% for each PDI of all levels involving chemotherapeutics (OR= 1.29; 95% CI: 1.01–1.66); and by 208% (OR= 3.08, 95% CI: 1.33–7.12) for each additional level 1 PDI involving chemotherapeutics (Table 5).

DISCUSSION

Prevalence

Our study confirms the high number of medications taken by patients with cancer, with the resulting PDI, and provides data more specific to patients above the age of 70. This is the first study to establish the incidence and severity of PDI and their association with severe chemotherapy adverse events in these patients.

In comparison with studies in general outpatient oncologic populations, our proportion of patients presenting PDIs is higher: Riechelmann et al. report a proportion of 27%, and van Leeuwen et al. report 58% of patients affected (14, 15). As in our study, all of van Leeuwen's patients did receive chemotherapy, whereas only 57% of Riechelmann's did. Our proportion of PDIs involving chemotherapy agents (29.2%) falls therefore closer to that of van Leeuwen (39%) than that of Riechelmann (13%). Our patients were older and taking a higher number of medications, so our results follow a logical trend. Using a 3-level severity ranking, Riechelmann et al (14) reported a proportion of severe PDI of 9%, and van Leeuwen 38%. Our 10.7% proportion of level 1 PDI falls within the same bracket. We elected to use the definition of PDI provided by our software version (Table 1) because it collectively accounts for timing of onset, level of severity, and level of documentation and thus offers a more comprehensive clinical picture of PDI. The PDI rates found in our study were also higher than those from non-cancer older adults, likely due to the increased exposure to polypharmacy and PDI of older patients with cancer receiving multidrug chemotherapy regimens and supportive medications. For example, in a Danish community sample Bjerrum et al. (34) found 25% PDI in participants 60–79 years old and 36% PDI in participants aged ≥ 80 years; while Hanlon et al. (35) found 35% PDI in a sample of VA outpatients aged ≥ 65 years.

Correlation with toxicity

The most notable and clinically relevant finding in our study is the relationship between PDI and chemotherapy-related toxicity. The risk of non-hematological toxicity increased by 17% for each additional level 1–3 PDI and by 29% for each additional PDI involving chemotherapeutics. It almost doubled for each additional level 1 PDI, and tripled for each additional level 1 PDI involving chemotherapeutics. These findings are critical for clinical practice and demonstrate that PDI should be routinely screened for before chemotherapy

initiation. Intervention studies in older adults demonstrated that drug regimens adjustments according to pharmacist's recommendations reduce polypharmacy, inappropriate prescribing, and adverse drug reactions (36–38). In the absence of a clinical pharmacist, a drug interaction software may be extremely helpful in the management of polypharmacy.

The risk of hematologic toxicity was not associated with PDI. Other research conducted at our institution found hematologic and non-hematologic toxicities influenced by different variables in older patients (29, 39, 40). Further exploration of the mechanisms involved is warranted.

One might argue that the number of PDIs is closely related to the level of comorbidity, and that our data simply reflect the association of increased risk of chemotherapy-related toxicity with higher comorbidity. We do not believe this to be the case. The relationship between comorbidity and chemotherapy related toxicity was explored with inconsistent results. In a large prospective community cohort of breast cancer patients, Shayne et al. (41) found a higher rate of dose delays and dose reductions in patients with more comorbidities. Frasci et al. (42) found that a Charlson Comorbidity score >2 was associated with a doubling of early chemotherapy interruption in patients with metastatic lung cancer. Using the same score, Hurria et al. found no association in one study and an association in another in breast cancer patients (30, 33) whereas Fader et al. (43) did not find an association in ovarian cancer patients. Grønberg et al. (44) found some partial correlation with comorbidity measured by the Cumulative Illness Rating Scale-Geriatric (CIRS-G), as patients with grade 3–4 comorbidities had higher rates of neutropenic infections and thrombocytopenia. The strongest data to date might be from two large prospective cohort studies aimed at designing predictive scores for toxicity from chemotherapy in the elderly. In none of them did comorbidity (measured by CIRS-G and OARS physical subscale respectively) arise as an independent contributor to the model (29, 32). Taken together, these results do not support a 2–3 fold relative risk of toxicity that would be uniquely linked to comorbidity. Therefore we believe our result truly represent, at least in part, a drug interaction effect.

Previous studies found that the number of drugs taken is correlated with the number of PDI, but also stressed that not all PDI are clinically relevant. Likewise, we found a strong correlation between total number of drugs and total number of PDI but no association between total number of PDI and complications of chemotherapy. Therefore, identifying and addressing PDI with high level of significance is paramount for improving therapy tolerance, as only considering the total number of drugs as a surrogate indicator of toxicity risk would be misleading.

PDI involving chemotherapeutics with high levels of clinical significance did have various mechanisms (Table 4). Some of these PDI may alter the exposure to the chemotherapeutics involved with consequent increased risk of chemotoxicity. The inhibition of the CYP-mediated metabolism of vincristine or cyclophosphamide by azole antifungal agents can increase their plasma levels and toxicity (45, 46). Increased toxicity from methotrexate can result from its reduced renal clearance induced by NSAIDs (47–49); and additive ototoxicity may result from the co-administration of cisplatin and furosemide (50, 51). Likewise, some of these PDI may affect the efficacy/toxicity of the non-chemotherapy drugs involved.

Conversely, pharmacokinetic interactions involving CYP-mediated metabolism or protein binding between warfarin and chemotherapeutics can alter the effects of warfarin with consequent increased risk of bleeding (52–55). Such interactions can occur even at low warfarin doses, particularly with fluorouracil (47). Our study might underestimate the impact of chemotherapy on prothrombin time stability, as this test is often conducted by the patients' primary physicians and would not have been available in the Moffitt records. Decreased plasma levels and efficacy of digoxin can occur when co-administered with cyclophosphamide or doxorubicin (56), or of phenytoin when co-administered with carboplatin (57).

Limitations

Our study used a drug interaction software rather than a formal review by a pharmacist. Although Comprehensive Cancer Centers might enjoy the availability of clinical pharmacists, most practicing oncologists are in need of simpler tools. The rapid rise of electronic records and prescription is a strong opportunity to use, at least as a first line, drug interaction softwares. Several drug interaction softwares are available, but unfortunately are not necessarily concordant in the way they rate the severity of drug interactions with chemotherapy (22). The results are drawn from a heterogeneous literature and focus on one to one drug interactions. The end-points vary and therefore render difficult the estimation of clinical relevance. A strength of our study is that it used a specific end-point: CTCAE rated severe toxicity, and took into account the number of interactions rated by the Drug Interaction Facts software. In this setting, we identified that the rating system used is clinically relevant for oncology patients. Its clear definitions and intuitive grading system (Table 1) are appealing to a clinician. Future studies should compare its performance with other drug interaction softwares, such as MicroMedex, Lexicomp, or OncoRx-MI. An essential feature of such softwares is the need for constant updating, as the number of drug used and the knowledge database evolves rapidly. Studies have compared softwares using pharmacists judgment on individual drug interactions with chemotherapy (58), but more “real life” studies with actual clinical endpoints such as effectiveness or side effects in patients taking multiple medications and adjusting for other predictors of chemotherapy tolerance (32, 59, 60) would be highly helpful in the geriatric oncology setting.

The retrospective design and the selected sample “enriched” for p450 metabolized drugs used in this study limit its generalizability and inferences. We were limited to toxicities spontaneously reported in the medical records. Although the software tested for all types of interactions, caution should be exerted when extrapolating our conclusions to regimens that do not contain at least one p450-metabolized drug, as other mechanisms of interaction exist (61). The majority of the presently used chemotherapy regimens do however contain p450-metabolized drugs. Biologic agents and targeted therapies should be studied separately, as they might not behave in the same way as classic chemotherapy drugs.

Drug Interactions Facts, like other softwares, assesses only one-to-one interactions. We showed previously that multiple drug interactions involving CYP modulation were associated with increased risk of chemotherapy –related toxicity risk, suggesting a potential synergistic effect (62).

Although patients do receive a geriatric assessment when initially seen in the SAOP, the chemotherapies studied were administered at different times during the management of the patients, and therefore the impact of geriatric assessment predictors on tolerance (29) could not be studied. Recent studies argue for integrating this aspect (29, 32, 60).

Conclusions

In conclusion, in a sample of cancer patients aged 70 years we found notable rates of PDI and a substantial association between high-level PDI and risk of non-hematological toxicity from chemotherapy. This is a call for oncologists to carefully review and trim down the list of medications of their older patients before initiating chemotherapy. The electronization of medical records and prescribing offers opportunities for an integrated use of drug interaction softwares. Since not all PDIs can be avoided, awareness of them might lead to chemotherapy adjustment or careful monitoring of side effects. Future research in this population comparing PDI softwares should confront them to well defined patient-centered end-points such as CTCAE toxicity, so that an integrated picture of the multidrug synergistic/antagonistic effects may be obtained. This research should also leverage toxicity risk prediction models integrating geriatric instruments such as the CARG and the CRASH scores (29, 32).

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Table 1

Definition of level of significance of potential drug interactions according to Drug Interactions 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.

Table 2

Sample characteristics: Baseline and chemotherapy data. Patient n=244.

Variable	
Age, years, median (range)	75 (70–91)
Female gender, N (%)	156 (63.9)
Tumor site, N (%)	
Breast	101 (41.4)
Non Hodgkin's lymphoma	33 (13.5)
Colorectal	23 (9.4)
Lung	17 (7.1)
Prostate	15 (6.1)
Other	55 (22.5)
Metastatic disease stage, N(%)	125 (51.2)
Number of medications, median (range)	11.5 (3 – 41)
BMI, kg/m ² mean (SD)	26.4 (4.9)
Blood pressure, mm Hg mean (SD)	138 (22)/74 (10)
ECOG PS, N(%)	
0	127 (52.0)
1	80 (32.8)
2	30 (12.3)
3	7 (2.9)
Baseline	
Albumin, g/dL (SD)	3.7 (0.4)
Bilirubin, mg/dL (SD)	0.5 (0.2)
AST, U/L (SD)	32.4 (18.8)
Creatinine clearance, mL/min (SD)	63.9 (22.9)
RBC count, 10 ⁶ /μL (SD)	4.1 (0.6)
MAX2, mean (SD)	0.62 (0.17)
Grade 3–4 non-hematological toxicity, %	126 (51.6)
Grade 4 hematological toxicity, %	66 (27.0)

Notes: Results are means and SD unless otherwise indicated. Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; AST, aspartate aminotransferase; RBC, red blood cell.

Table 3

Types and frequency of potential drug interactions identified

Potential drug interaction classification	Involving all drugs (N= 769)	Patients affected (N= 184)	Involving chemotherapy drugs (N= 225)	Patients affected (N=112)
	N (% [*])	N (% ^{**})	N (% [*])	N (% ^{**})
Level 1	82 (10.7)	52 (21.3)	32 (14.2)	25 (10.2)
Level 2	286 (37.2)	126 (52.0)	25 (11.1)	16 (6.6)
Level 3	22 (2.8)	19 (7.8)	0 (0.0)	0 (0.0)
Level 4	274 (35.6)	137 (56.1)	136 (60.4)	87 (35.6)
Level 5	105 (13.6)	77 (31.6)	31 (13.8)	31 (12.7)

Note:

* Represents percentage of the total number of potential drug interactions;

** Represents percentage of total patients in the sample (N=244).

Table 4

Most frequent level 1–2 potential drug interactions involving chemotherapeutics: description of potential clinical outcomes and of potential underlying mechanisms

Level	Drug dyads	N	Potential outcomes and mechanisms
1	Cyclophosphamide/Paclitaxel/Capecitabine/Etoposide/Fluorouracil/Carboplatin- Warfarin	28	Increased effect of warfarin due to protein displacement, inhibition of warfarin metabolism, or inhibition of clotting factor synthesis (52–54)
	Vincristine- Azole antifungal drugs		Inhibition of CYP3A4-mediated metabolism of vincristine by azole antifungal agents resulting in increased risk of vincristine toxicity (45)
	Methotrexate- NSAID	2	Reduced renal clearance of methotrexate induced by NSAID resulting in increased risk of methotrexate toxicity (63)
2	Cyclophosphamide/Doxorubicin/Methotrexate/Vincristine- Digoxin	17	Reduced digoxin serum levels due to drug-induced alterations in the intestinal mucosa that result in reduced digoxin absorption (56)
	Cyclophosphamide- Fluconazole		Increased exposure to cyclophosphamide and risk for toxicity resulting from the fluconazole-mediated inhibition of cyclophosphamide hepatic metabolism (46)
	Cisplatin- Furosemide	2	Additive ototoxicity; unknown mechanism (50, 51)
	Carboplatin- Phenytoin	1	Decreased absorption, protein displacement, and increased hepatic metabolism of phenytoin resulting in decreased serum levels and effect (64)

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme; CYP3A4, cytochrome P450 3A4.

Table 5

Logistic regression models predicting likelihood of experiencing grade 3–4 non-hematological toxicity (in bold, $p < 0.05$)

Main predictor	OR	95% CI	R ²
Level 1–5 PDI	1.07	0.99–1.17	0.13
Level 1–3 PDI	1.17	1.01–1.35	0.14
Level 1 PDI	1.94	1.22–3.09	0.16
Level 2 PDI	1.13	0.94–1.36	0.13
Level 1–5 PDI involving chemotherapeutics	1.29	1.01–1.66	0.14
Level 1–2 PDI involving chemotherapeutics	1.61	0.99–2.64	0.14
Level 1 PDI involving chemotherapeutics	3.08	1.33–7.12	0.16
Level 2 PDI involving chemotherapeutics	1.04	0.57–1.90	0.13

Note: All models are adjusted for age, gender, body mass index, blood pressure, Eastern Cooperative Oncology Group performance status, aspartate aminotransferase, albumin, bilirubin, creatinine clearance, red blood cell count, stage, and MAX2.