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Pharmacological profile and potential drug interactions in ovarian cancer hospitalized patients

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Abstract

The aim of this study was to identify the main therapeutic classes prescribed to ovarian cancer patients and the potential drug interactions (PDI) during hospitalization. This descriptive retrospective work was carried out in a referral gynecological cancer hospital from the Brazilian public health system. The first 24 h inpatients' prescriptions were evaluated to obtain the pharmacological profile data. Clinical and epidemiological characteristics were collected through the analysis of electronic medical records. A total of 236 patients were included in the study, of which 154 (65.25%) had PDI, with a mean of 1.43 ± 1.76 interactions per patient. The main therapeutic classes prescribed were analgesics and antiemetics (35%), compatible with the oncologic supportive care. All PDI identified ($n = 331$) were categorized by severity, using the Micromedex database, resulting in: 1.51% contraindicated, 67.67% major, 24.77% moderate, and 6.04% minor. The more prevalent PDI were ondansetron/tramadol (22.05%) and metoclopramide/tramadol (7.25%), both major. An association between PDI and polypharmacy was observed, which did not occur between age or length of stay. Ongoing prescription review by the pharmaceutical team is necessary to identify, monitor, and manage PDI-related adverse events and carry out required interventions with patients, physicians, and nurses. Taken together the data showed that even in a specialized hospital, the complexity of the pharmacotherapy can cause harm to the ovarian cancer patient. The clinical pharmacist acting in a multidisciplinary team is important for improving patient safety in oncology services.

Keywords

Drug interactions, cancer patient, pharmaceutical care

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Introduction

Drug interactions are considered a phenomenon that occurs when the effects and/or toxicity of a drug are altered by the presence of another drug or food, which may be desirable or undesirable.[1] Beneficial or desirable drug interactions aim to treat concomitant diseases, reduce adverse effects, prevent or delay the onset of bacterial resistance, increase treatment adhesion, and increase efficacy or allow dose reduction. On the other hand, harmful or undesirable interactions are those that cause a reduction in the effect or a result contrary to what is expected, increasing the incidence and range of adverse effects and consequently the cost of therapy.[2,3] Scientific information on the incidence of drug interactions is in many cases divergent, mainly due to the difference in the methodology applied and the differences in the interpretation of clinical relevance.[4] Drug interactions can broadly be classified as physical-chemical, pharmacodynamic, and pharmacokinetics.[5] Most clinically relevant pharmacokinetic interactions occur in the metabolization phase due to the action of cytochrome P 450 enzymes (CYP 450). CYP 450 enzymes have the function of metabolizing several drugs, including those widely used in the hospital environment.[6] CYP 450 enzyme inhibitors and inducers differ in their selectivity for the different isoforms of this enzyme. Another aspect to be considered is that most drugs are eliminated almost entirely by the kidneys, so the excretion rate of various agents can be modified through interactions along the nephron. Changes in urinary pH

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interfere with the degree of ionization of weak acids and bases, also affecting the pharmacological response. The competition of drugs in the proximal tubule for tubular secretion is another mechanism that alters the time of action of some medications.[7] Another important pharmacokinetic interaction is the inhibition of ABCB1 (Glycoprotein-P) flow transporters, which results in the change in the bioavailability of several chemotherapy drugs.[8] Cancer patients often present physiological changes due to their pathophysiology that may cause deviations in the pharmacokinetic and pharmacodynamic profiles of drugs. These modifications represent a great challenge for the pharmacotherapeutic approach of the patients.[9–11]

Given the above and considering the lack of studies in cancer patients, specifically in patients diagnosed with ovarian cancer, the present study aimed to identify the main pharmacological classes used during its hospitalization and the potentials of clinically relevant drug interactions.

Patients and methods

Study design

This observational and retrospective study was conducted at the Brazilian National Cancer Institute José Alencar Gomes da Silva (INCA-II), belonging to the Public Health System, and specialized in the treatment of gynecological cancer. To identify the pharmacological profile and potential drug interactions, we evaluated the first 24 h prescription of ovarian cancer patients, admitted in one year. The inclusion criteria of the study were: patients diagnosed with ovarian cancer, under cancer treatment, aged 18 years or older. Were excluded the patients that had less than 2 medications prescribed in the first 24 h of hospitalization. Clinical and epidemiological characteristics (tumor type, age, and length of stay) were collected through the analysis of electronic medical records. As well as pharmacological profile information was collected from the medical prescriptions (medication, dose, posology, time of treatment, route of administration, and time of administration). The drugs were categorized according to *Anatomical Therapeutic Chemical* (ATC) classification system. To verify the potential drug interactions, the monographs of the drugs were researched in the *DrugReax database* ® Micromedex System.

Throughout the study, patients were identified using a growing sequence of alphanumeric codes drawn up by the researchers to ensure the anonymity of the research participants. The study was approved by the ethics committee of the National Cancer Institute José Alencar Gomes da Silva, CAAE no. 26364514.0.0000.5274.

Statistical analysis

The statistical analysis of the data was processed through the GraphPad Prism 9 Software, and Microsoft Excel, 2016. Quantitative variables were expressed as mean and standard deviation. Statistical tests were applied with 95% confidence and the results will be presented in table and graphs form. The correlation was estimated by Pearson's coefficient.

Results

A total of 236 ovarian cancer patients were included in the study. The mean age of the patients was 56.34 ± 15.07 years, ranging from 19 to 98 years. The length of stay ranged from 1 to 68 days, with a general average of 10.17 ± 9.74 days. Regarding the total number of drugs prescribed, 8.05% of the patients had less than five drugs prescribed in the first 24 h, while 91.95% had five or more medications in the prescription, with an average of 8.55 ± 2.84, according to Table 1.

According to the Anatomical Therapeutic Chemical Classification (ATC), drugs related to the nervous system were more frequently prescribed (32.65%), followed by the alimentary tract and metabolism system (29.85%), the cardiovascular system (24.85%), blood and blood-forming organs (6.18%), anti-infectives for systemic use (4.56%), hormonal preparations (1.76%), skeletal muscle system (0.17%) and respiratory system (0.15%). Most drugs prescribed to ovarian cancer inpatients were described in Table 2.

Of the 236 patients analyzed, 154 (65.25%) presented PDI in the prescription, with an average of 1.43 ± 1.76 PDI per patient. PDIs ($n = 331$) severity classification were shown in Table 3.

The drugs most involved in the PDI were ondansetron, tramadol, metoclopramide, captopril, omeprazole, diazepam, and hydrochlorothiazide. Antineoplastic agents were not identified in the analyzed prescriptions, since most of the chemotherapy treatment at the study hospital is performed on an outpatient basis. In the local of study, the patients are mainly hospitalized for surgical treatment or clinical support. Table 4 shows the main PDI of ovarian cancer inpatients, describing its severity, possible mechanism, and clinical consequence.

Table 1. Epidemiological and clinical characteristics of hospitalized patients diagnosed with ovarian cancer.

Epidemiological and Clinical Characteristics	Values
Patients (n)	236
Age (mean ± DP), years	56.34 ± 15.07
< 60 years old (%)	58.9
≥ 60 years old (%)	41.1
Length of stay (mean ± DP), days	10.17 ± 9.74
Number of drugs (mean ± DP)	8.55 ± 2.84
Patients with < 5 drugs (%)	8.05
Patients with ≥ 5 drugs (%)	91.95

Table 2. Anatomical therapeutic chemical classification (ATC) of the main drugs used in hospitalized patients diagnosed with ovarian cancer.

Anatomical main group and Therapeutic subgroup	Drugs	ATC classification	(%) n = 680
Alimentary tract and metabolism		*A*	29.85
Drugs for acid related disorders	Ranitidine	A02BA02	0.29
	Omeprazole	A02BC01	4.41
Drugs for functional gastrointestinal disorders	Butylscopolamine	A03BB01	0.44
	Metoclopramide	A03FA01	4.12
Antiemetics and antinauseants	Ondansetron	A04AA01	15.44
Drugs for constipation	Bisacodyl	A06AG02	0.29
Drugs used in diabetes	Insulin (human)	A10AC01	2.21
	Insulin (human) NPH	A10AC01	2.50
	Metformin	A10BA02	0.15
Blood and blood-forming organs		*B*	6.18
Antithrombotic agents	Enoxaparin	B01AB05	0.44
	Acetylsalicylic acid	B01AC06	0.29
Antianemic preparations	Ferrous sulfate	B03AA07	0.44
Blood substitutes and perfusion solutions	Electrolytes	B05BB01	2.50
	Potassium chloride	B05XA01	2.50
Cardiovascular system		*C*	24.85
Antihypertensives	Methyldopa	C02AB01	0.29
	Clonidine	C02AC01	1.18
Diuretics	Hydrochlorothiazide	C03AA03	3.38
	Furosemide	C03CA01	1.03
	Spironolactone	C03DA01	0.29
Beta blocking agents	Propranolol	C07AA05	0.74
	Atenolol	C07AB03	1.32
	Carvedilol	C07AG02	0.15
Calcium channel blockers	Amlodipine	C08CA01	0.29
	Verapamil	C08DA01	0.29
Agents acting on the renin-angiotensin system	Captopril	C09AA01	12.50
	Enalapril	C09AA02	0.74
	Losartan	C09CA01	2.21
Lipid modifying agents	Simvastatin	C10AA01	0.44
Systemic hormonal preparations. excl. sex hormones and insulins		*H*	1.76
Pituitary and hypothalamic hormones and analogs	Octreotide	H01CB02	0.15
Corticosteroids for systemic use	Dexamethasone	H02AB02	0.59
Thyroid therapy	Levothyroxine sodium	H03AA01	1.03
Antiinfectives for systemic use		*J*	4.56
Antibacterials for systemic use	Clarithromycin	J01FA09	0.15
	Ciprofloxacin	J01MA02	2.65
	Moxifloxacin	J01MA14	0.29
	Metronidazole	J01XD01	1.47
Musculoskeletal system		*M*	0.15
Antigout preparations	Allopurinol	M04AA01	0.15
Nervous system		*N*	32.65
Anesthetics	Fentanyl	N01AH01	1.03
Analgesics	Morphine	N02AA01	3.09
	Codeine and Paracetamol	N02AJ06	0.15
	Tramadol	N02AX02	16.32
Antiepileptics	Phenytoin	N03AB02	0.74
	Gabapentin	N03AX12	0.29
Anti-parkinson drugs	Biperiden	N04AA02	0.29
Psycholeptics	Chlorpromazine	N05AA01	1.32
	Haloperidol	N05AD01	1.62
	Diazepam	N05BA01	3.82
	Bromazepam	N05BA08	0.15

(continued)

Table 2. Continued.

Anatomical main group and Therapeutic subgroup	Drugs	ATC classification	(%) n = 680
	Midazolam	N05CD08	0.44
Psychoanaleptics	Amitriptyline	N06AA09	1.32
	Citalopram	N06AB04	1.47
	Escitalopram	N06AB10	0.44
	Sertraline	N06AB06	0.15
Respiratory system		*R*	0.15
Antihistamines for systemic use	Promethazine	R06AD02	0.15

NPH: neutral protamine hagedorn

Table 3. Classification of PDI, according to the severity (by *DrugReax database* ®Micromedex System).

PDI Classification	n	%
Contraindicated	5	1.51
Major	224	67.67
Moderate	82	24.77
Minor	20	6.04
TOTAL	331	100

The contraindicated PDI, most found in prescriptions, were the associations of amitriptyline and metoclopramide, and citalopram and metoclopramide. While the major PDI were to the associations of ondansetron and tramadol, metoclopramide and tramadol, and captopril and potassium chloride.

The statistical analysis showed that the number of PDI increases significantly with the rise in the number of drugs (Figure 1). The correlation between the PDI and the number of drugs used by patients was evaluated using Pearson's correlation coefficient ($r = 0.5971$, $p < 0.0001$,). However, there was no association between age ($p = 0.3335$) or length of stay ($p = 0.8254$) with the potential for interactions.

Discussion

Few studies have been conducted to evaluate the risk and profile of PDI in gynecological cancer patients, specifically in the ovarian cancer population this is missing data in Brazil. In the two hundred and thirty-six patients evaluated in this study, one hundred and fifty-four (65.25%) had PDI, of which 67.67% were classified as major severity. The presence of PDI can contribute to the occurrence of undesirable adverse effects, especially in unfavorable clinical conditions, such as the presence of comorbidities, age, polypharmacy, physiological changes associated with the disease or treatment.[8]

In many cases, cancer patients present alterations in liver and/or kidney function due to chemotherapy treatment or deterioration of their clinical condition.[8] These changes interfere in all pharmacokinetic phases, mainly in the distribution and metabolization of drugs.[12] Mechanisms of drugs absorption also can be influenced in several ways due to changes in peristaltic bowel movements, as well as the presence of mucositis, and even by the nutritional status of the patients.[11,12] Changes in the skin, muscles, and hydration of the body may alter the absorption of drugs administered intramuscularly, subcutaneously, and transdermally.[13] Renal clearance of drugs can be greatly impaired in cancer patients due directly or indirectly kidney damage.[14,15] Another important issue is hypoxia and peripheral ischemia that cause a reduction in tissue pH and endothelial lesions. Pharmacokinetic and pharmacodynamic changes caused by tissue pH change have not been extensively studied. Decreased capillary permeability and renal failure contribute to a reduction in circulating albumin fraction. The reduction in plasma protein concentration radically alters the rate of drug-protein binding.[9] The oncologic patient usually presents variation in the volume of distribution of the drug due to the reduction of plasma protein levels and generalized edema.[11] In this line of reasoning, changes in plasma protein concentration can lead to unexpected pharmacological effects. The increase of the free fraction of a drug can cause toxic levels, these changes become clinically important for drugs with a high rate of binding and with narrow therapeutic index.[16,17] For all these described reasons, a careful evaluation of the patient's pharmacological therapy, including the concomitant use of antineoplastic agents, supportive care drugs, and medications for chronic diseases is essential to obtain the desired outcome.

In this study, the identified PDIs included supportive care medications and medications related to the treatment of chronic diseases, since antineoplastic agents were not present in the examined prescriptions. This fact can be explained by the hospital standard of outpatient chemotherapy treatment. The PDIs were detected through Micromedex® Program, whose sensitivity is considered high.[18, 19]

Regarding the pharmacotherapeutic approach of these patients, the main drugs prescribed were analgesics (19.56%), agents acting on the renin-angiotensin system (15.45%), and antiemetics and antinauseants (15.44%).

Table 4. The top fifteen PDI found in the prescriptions of patients with ovarian cancer.

PDI	Severity	N	Interaction Effect	Clinical Management
Ondansetron/ Tramadol	Major	73	Concurrent use of Tramadol and serotonergic agents may result in an increased risk of serotonin syndrome. Probable Mechanism: additive serotonergic effects.	Monitor the patient, particularly during the first few days of treatment, and discontinue tramadol if serotonin syndrome is suspected
Metoclopramide/ Tramadol	Major	24	Concomitant use of metoclopramide and a CNS depressant (eg, sedatives, hypnotics, opiates, and anxiolytics) may result in an increased risk of CNS depression and should be avoided. Probable Mechanism: additive pharmacologic effect.	Monitor to adverse effects
Diazepam/ Omeprazole	Minor	16	Concurrent use of Omeprazole and Diazepam may result in enhanced and prolonged diazepam effects. Probable Mechanism: inhibition by omeprazole and metabolites of diazepam metabolism.	Monitor excessive benzodiazepine effects (eg, sedation, dizziness, ataxia, weakness, decreased cognition, or motor performance). If necessary, reduce the diazepam dose or switching to a benzodiazepine eliminated by glucuronidation (lorazepam, oxazepam, temazepam).
Captopril/ Hydrochlorothiazide	Moderate	14	Concurrent use of ace inhibitors and Thiazide diuretics may result in a reduction of blood pressure. Probable Mechanism: vasodilation and relative intravascular volume depletion.	Before the ACE inhibitor therapy, decreasing the diuretic. If not possible, reduce the ACE inhibitor starting dose
Captopril/ Potassium Chloride	Major	13	Concurrent use of Potassium and Captopril may result in hyperkalemia. Probable Mechanism: lowered aldosterone levels.	Monitor serum potassium levels for persistent elevations, especially in patients with renal dysfunction, or elderly.
Captopril/ Lactated Ringers Injection	Major	10	Concurrent use of Potassium and Captopril may result in hyperkalemia. Probable Mechanism: lowered aldosterone levels	
Captopril/ Losartan	Major	10	Concurrent use of Angiotensin-converting enzyme inhibitors and Angiotensin II receptor blockers may result in an increased risk of adverse events (ie, hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure). Probable Mechanism: dual blockade of the renin-angiotensin-aldosterone system.	Conduct closely monitor of blood pressure, renal function, and electrolytes
Captopril/ Insulin	Moderate	9	Concurrent use of Ace inhibitors and Antidiabetic agents may result in an increased risk of hypoglycemia.	Conduct more frequent glucose monitoring, both during treatment and after withdrawal of an ACE inhibitor. If necessary, adjust the Insulin dose.
Captopril/ Insulin NPH	Moderate	9	Concurrent use of Ace inhibitors and Antidiabetic agents may result in an increased risk of hypoglycemia.	

(continued)

Table 4. Continued.

PDI	Severity	N	Interaction Effect	Clinical Management
Ciprofloxacin/ Ondansetron	Major	7	Concurrent use of Ciprofloxacin and Ondansetron may result in an increased risk of QT interval prolongation. Probable Mechanism: additive effects on the QT interval.	Susceptible patients may require ECG monitoring
Haloperidol/ Ondansetron	Major	5	Concurrent use of Haloperidol and Ondansetron may result in an increased risk of QT interval prolongation. Probable Mechanism: additive effects on QT interval prolongation	
Metronidazole/ Ondansetron	Major	5	Concurrent use of METRONIDAZOLE and QT INTERVAL PROLONGING DRUGS may result in an increased risk of QT-interval prolongation and arrhythmias. Probable Mechanism: additive QT-interval prolongation.	
Levothyroxine/ Omeprazole	Moderate	5	Concurrent use of Levothyroxine and proton pump inhibitors may result in decreased levothyroxine effectiveness. Probable Mechanism: decreased levothyroxine absorption.	Administer levothyroxine 4 h before or after omeprazole
Amitriptyline/ Metoclopramide	Contraindicated	2	Concurrent use of Metoclopramide and Tricyclic antidepressants may result in an increased risk of extrapyramidal reactions and neuroleptic malignant syndrome.	Monitor patients closely for signs and symptoms (fever, sweating, confusion, muscle stiffness). If symptoms occur, discontinue both agents and manage medically.
Citalopram/ Metoclopramide	Contraindicated	1	Concurrent use of Metoclopramide and SSRIs may result in an increased risk of extrapyramidal reactions and neuroleptic malignant syndrome.	

ACE: Angiotensin-converting enzyme; CNS: central nervous system; ECG: electrocardiogram; QT-interval: length of time between the start of the Q-wave and the end of the T-wave in the ECG; SSRIs: selective serotonin reuptake inhibitors.

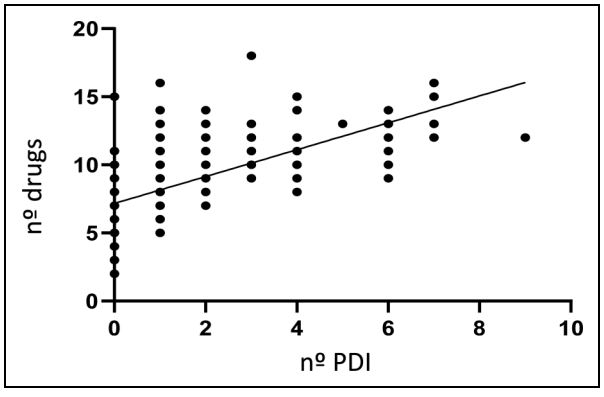

Figure 1. Correlation between the number of potential drug interactions and the number of prescribed drugs. The correlation between the number of PDI and the number of drugs in the patient prescription (n = 236) was assessed using Pearson's correlation coefficient (r = .5971. p < .0001).

The main PDI detected was the association of ondansetron and tramadol, two drugs widely used in cancer patients, for the treatment of emesis and pain control, respectively.[20] The clinical management of this pharmacodynamic PDI can be the replacement of one of the drugs, but if coadministration is necessary, the recommendation is to maintain constant monitoring to identify adverse reactions and discontinue tramadol if serotonin syndrome was suspected.[19]

Many cancer patients develop psychological problems such as insomnia, depression, and nausea, requiring the use of medications that act at the central nervous system (CNS) level.[21,22] These data corroborated our findings, in which 32.65% of the prescribed drugs were classified as acting on the nervous system. All contraindicated PDI detected in this study were related to medications for the nervous system (Amitriptyline/Metoclopramide, Citalopram/ Metoclopramide, Biperiden/ Lactated

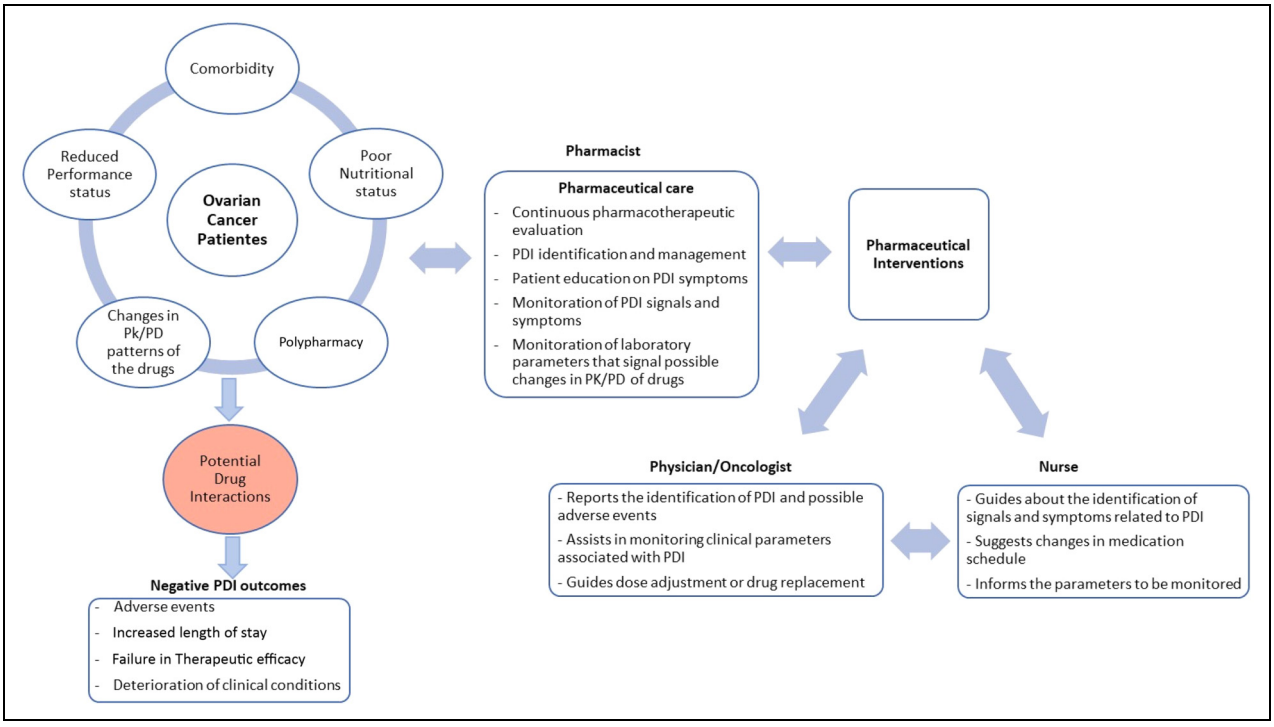

Figure 2. Characteristics of ovarian cancer patients that favor the occurrence of PDI and the role of the clinical pharmacist in preventing negative PDI outcomes. Comorbidities, polypharmacy, reduced performance status, poor nutritional status, and physiological changes with consequent changes in drug Pk/PD patterns are common features seen in ovarian cancer patients that may confer an increased risk of PDI. The clinical pharmacist in the multidisciplinary team plays an important role in preventing, detecting, and early management of negative PDI outcomes through patient education, guidance, and interventions with other healthcare team members, such as oncologists and nurses. PDI: Potential Drug Interaction; PK/PD: pharmacokinetics and pharmacodynamics.

Ringers Injection, Biperiden/ Potassium Chloride), been necessary constant supervision of the prescriptions to prevent this association.[19]

In a study developed by Sales et al. (2019) the drugs most used by the patients were losartan, hydrochlorothiazide, omeprazole, metformin, and simvastatin, been also highlighted the drugs that act in the nervous system such as amitriptyline and escitalopram.[23] Our study revealed a high prevalence of tramadol, ondansetron, captopril, omeprazole, metoclopramide, diazepam, and hydrochlorothiazide in the prescriptions. About 91.95% of ovarian cancer patients had at least five drugs prescribed. In cancer patients, the prescription of multiple drugs is often necessary, which requires a detailed review of pharmacotherapy to detect and prevent drug-related problems.[24,25]

An elevated number of PDI represents an independent risk factor for unplanned hospitalization and was associated with readmission in cancer patients.[26,27] In this study were observed a correlation between the number of potential drug interactions and the number of drugs prescribed, suggesting that the number of drugs prescribed is a predictive factor that increases the risk of interactions in hospitalized patients, following the trend of other studies[28–30] However, there were no differences in the rates of potential for drug interaction in relation to age and time of hospitalization.

The prevention, early identification, and management of PDI are essential to minimize harm to the patients, and costs for the health system. Therefore, the role of the clinical pharmacist in the multidisciplinary team is essential for the quality of oncology care.[27] The characterization of the most recurrent PDI in the institution is extremely important to support the actions of the clinical pharmacist, who can define trigger tools to identify the main drug associations to be avoided and/or monitored.

In Brazil, the RDC N° 220 of 2004, published by the National Health Surveillance Agency (ANVISA), was an important milestone for patient safety regarding the use of medications, as it established the need for a multidisciplinary team in antineoplastic therapy services, including the mandatory action of the pharmaceutical professional.[31,32]

Given the characteristics of the cancer patient, such as polypharmacy, presence of comorbidities, and physiological changes associated with the disease and/or its treatment, the medication therapy management by the clinical pharmacist is an important tool to increase the safety and effectiveness of the therapeutic plan. Working in the multidisciplinary team, the pharmacist can review drug therapy and minimize

the effects of PDI, through patient education and interventions with oncologists and nurses (Figure 2).

As a limitation of this study, we can mention the fact that it was unicentric, for a better understanding it is suggested that multicenter studies be carried out in the future. Additionally, the clinical manifestations of drug interactions were not evaluated, so it was called potential interactions.

Conclusion

The study showed the elevated risk of PDI in ovarian cancer inpatients, even between non-antineoplastic drugs. Tightly pharmacological monitoring in this population is very important to maximize the pharmacotherapeutic benefits and minimize complications arising from PDI. In this context, it is imperative the presence of the clinical pharmacist working in a multidisciplinary team to prevent, detect and manage these possible interactions in oncology services.

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