Polymedication in Elderly Submitted to Oncological Treatment

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Polimedicação em Idosos Submetidos a Tratamento Oncológico

Polimedicación en Personas Mayores Recibiendo el Tratamiento Oncológico

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Abstract

Introduction: The elderly patient with cancer has potential risk of polymedication due to the increase of comorbidity and complexity of the cancer treatment, which often includes multiple antineoplastic and supportive medications. **Objective:** The objective is to identify the frequency of polypharmacy, potentially inappropriate medication use and drug interaction in elderly patients with cancer. **Method:** It were collected sociodemographic, pharmacological and clinical information from 20 elderly patients (≥ 65 years) with cancer, polymedicated (≥five drugs), from July to August 2016, in an outpatient clinic in São Luís, MA through electronic chart and questionnaires applied in interviews. To analyze the data, it were used the: Anatomical Therapeutic Chemical (ATC), Micromedex®, Drugs®, Lexicomp® and the Anfarmag Phytotherapy Guideline. Beers Criteria 2015 was used to identify potentially inappropriate medication for the elderly. **Results:** Among the patients, 70% were males, with a mean age of 73 years (SD=7.9). The most prevalent types of cancer were prostate cancer and breast. Cardiovascular and endocrine comorbidities were the most reported. A total of 134 drugs prescribed and self-medication were identified, of which 41 were antineoplastic. Eighty percent of the patients were exposed to potential risk of drug interaction, totaling 90 (63.2% of moderate, 21.2% of significant and 8.8% of mild severity). There were 4 interactions involving medicinal plants and seven inappropriate medications in use by 20% e 65% of the elderly patients, respectively. **Conclusion:** Among the patients included in this study, it was verified the occurrence of polypharmacy, potential drug interactions and the use of potentially inappropriate medications for the elderly.

Key words: Polypharmacy; Neoplasms/drug therapy; Antineoplastic Agents; Aged.

Resumo

Introdução: O paciente idoso com câncer possui risco potencial de polimedicação pelo aumento de comorbidade e complexidade do tratamento do câncer que, muitas vezes, inclui múltiplos antineoplásicos e medicamentos de suporte. **Objetivo:** Identificar a frequência de polimedicação, o uso de medicamentos potencialmente inapropriados e a interação medicamentosa em pacientes idosos com câncer. **Método:** Coletaram-se informações sociodemográficas, farmacológicas e clínicas de 20 pacientes idosos (≥65 anos) com câncer, polimedicados (≥cinco medicamentos), de julho a agosto de 2016, em um ambulatório em São Luís – MA, por meio de prontuário eletrônico e questionários aplicados em entrevistas. Para análise dos dados, utilizaram-se as ferramentas: Classificação Anatômica Terapêutica Química, Micromedex®, Drugs®, Lexicomp® e o Manual de fitoterápicos da Anfarmag. O *Beers Criteria* 2015 foi utilizado para identificação dos medicamentos potencialmente inapropriados para idosos. **Resultados:** Entre os pacientes, 70% eram do sexo masculino, com idade média de 73 anos (DP=7,9). Os tipos de câncer mais prevalentes foram os de próstata e mama. Quanto às comorbidades, as cardiovasculares e as endócrinas foram as mais relatadas. Foram identificados 134 medicamentos prescritos e de automedicação, dos quais, 41 eram antineoplásicos. Oitenta por cento dos pacientes estavam expostos a risco potencial de interação medicamentosa, totalizando 90 (63,2% de gravidade moderada, 21,2% importante e 8,8% menor). Detectaram-se quatro interações envolvendo plantas medicinais e sete medicamentos inapropriados para idosos em 20% e 65% dos pacientes, respectivamente. **Conclusão**: Entre os pacientes incluídos neste estudo, verificou-se a ocorrência de polimedicação, de interações medicamentosas potenciais e do uso de medicamentos potencialmente inapropriados para idosos.

Palavras-chave: Polimedicação; Neoplasias/tratamento farmacológico; Antineoplásicos; Idoso.

Resumen

Introducción: Un paciente con cáncer de edad avanzada tiene riesgo potencial de polmedicación debido a mayor comorbilidad y complejidad del tratamiento del cáncer, que incluye múltiples medicamentos antineoplásicos y de soporte. **Objectivo**: Identificar la frecuencia de polifarmacia, de uso de medicamentos potencialmente inapropiados y interacciónes medicamentosa en personas mayores con cancro. **Método**: En el período de julio a agosto de 2016, en ambulatorio en São Luís – MA, se recolectó informaciones sociodemográficas, farmacológicas y clínicas de 20 pacientes ancianos (≥ 65 años) cancro, polimedicados (≥ cinco medicamentos), por medio de recolección en registro médico electrónico y cuestionarios. Para análisis de datos, se utilizaron herramientas como Clasificación Anatómica Terapéutica Química, Micromedex®, Drugs®, Lexicomp® y Manual de fitoterápicos de la Anfarmag. *Beers Criteria* 2015 se utilizó para identificar los medicamentos potencialmente inapropiados para ancianos. **Resultados:** Entre los pacientes, 70% eran del sexo masculino, con edad promedio de 73 años (DP=7,9). Los tipos de cancro más prevalentes fueron de próstata y mama. En cuanto a las comorbilidades, las cardiovasculares y endocrinas fueron las más relatadas. Se identificaron 134 prescripciones y automedicación, de los cuales 41 antineoplásicos. 80% de pacientes estaban expuestos a interacción medicamentosa, totalizando 90 (63,2% de gravedad moderada, 21,2% importantes y 8,8% leves). Se detectaron 4 interacciones que involucra plantas medicinales y siete medicamentos inapropriados para ancianos en el 20% y 65% de los pacientes, respectivamente. **Conclusión:** Entre los pacientes incluidos en estudio, verificamos aparición de polifarmacia, riesgos de posibles interacciones medicamentosas y el uso de medicamentos potencialmente inapropiados para los ancianos.

Palabras clave: Polifarmacia; Neoplasias/tratamiento farmacológico; Antineoplásicos; Ancianos.

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INTRODUCTION

Brazil is in process of demographic ageing and consequent increase of demand for health services[1]. According to the Brazilian Institute of Geography and Statistics (IBGE), the Brazilian population tends to grow in the next decades. It is estimated that in 2043 a quart of the Brazilian population will be older than 60 years[2]. According to Nunes et al.[3], the Longitudinal Study of the Health in Brazilian Elderly (ELSI-BRASIL) identified that, in a total of 9,412 individuals, 67.8% were in the age range of 65-69 years and presented two or more diseases[3].

In 2016, non-communicable diseases (NDC) accounted for 74% of the total deaths in Brazil, with emphasis in cardiovascular diseases (28%) and malignant neoplasms (18%)[4]. The elderly are more susceptible to cancer because of years of exposure to cancer agents, reduction of the parameters of cellular reparation and presence of morbidities[5]. Elderly patients with cancer in treatment with antineoplastic present toxicities that demand support medication to manage them, contributing to polypharmacy[6].

Polypharmacy or polymedication is commonly seen in elderly patients and can be qualitative, when related to prescription or use of more medications that what is clinically indicated to the patient and quantitative, when it is related to the number of medications consumed[7]. The term polypharmacy is associated to many negative consequences as non-adherence to the treatment, drugs interactions and increase of health costs[8].

Despite the possible negative effects, polypharmacy can be necessary for patients with clinical conditions, where pharmacotherapy was optimized and prescribed with better scientific evidence available, with the purpose of offering better quality of life to the patient and increase its survival[9]. The potentially inappropriate medications (PIM) for elderly are drugs associated to the risk of causing side effects greater than the benefits, are not cost-effective and there are available options to replace them. Even with several evidences demonstrating the risks of PIM, they are still prescribed and many times, chosen as first line treatment[10].

Drug interaction can be defined as a clinical event where actions and effects of a drug are altered by the presence of another drug, phytotherapic or food. When administered concomitantly, can act independently or interact, reducing or increasing the therapeutic or toxic effects[11].

Based in the aforementioned and considering the paucity of studies about the theme, specifically in Brazilian elderly with cancer, the present study had the objective to identifying the frequency of polypharmacy, the use of PIM and possible clinically relevant drug interactions in elderly patients with cancer in an oncology ward in a hospital located in the municipality of São Luís – MA.

METHOD

Multiple cases, descriptive, non-comparative study, with sample by convenience of 20 patients ≥ 65 years, of both genders submitted to oncologic treatment in the chemotherapy ward of a private hospital in the municipality of São Luís, Maranhão. The following inclusion criteria were considered: patients accepted to respond to the questionnaire, signature of the Informed Consent Form, age ≥ 65 years, any type of cancer and in oncologic treatment with oral and/or intravenous medication. The exclusion criteria were patients with non-melanoma skin cancer for not being treated with chemotherapy and presence of cognitive deficit that hampered the understanding of the information.

From August to September 2016 data were collected in two interviews because of the time needed to collect and because it was appropriate to offer the service and obtain data about the drugs.

In the first interview, a questionnaire developed by the investigators to obtain sociodemographic data, comorbidities and pharmacologic information as dose, presentation, posology and time of use about the medications of continuous use – without prescription, self-medication, supplements, antineoplastic, hormone therapy and phytotherapy. The patients were requested to bring this medication in the second interview.

The medication mentioned by the patients were classified according to the Anatomical Therapeutic Chemical (ATC) adopted by the World Health Organization (WHO)[12], pursuant to level one, which classifies the drugs per organs and systems where they act. Polypharmacy was defined as the utilization of five or more medications as defined by the National Comprehensive Cancer Network[13]. Only quantitative analysis of polypharmacy was performed, not qualitative.

Drug interactions were searched and evaluated in the databases: Micromedex Solutions®, Drugs®, Lexicomp® and the information obtained from each one were compared. For such, antineoplastic drugs used at home and at the ward were crossed with drugs used to treat comorbidities and support for each patient. For classification of severity, it was utilized Micromedex®, that classifies the interactions in counter-indicated, important, moderate and secondary (mild). In this study, it were identified drug interactions of important, moderate and secondary severity; it were not identified counter-indicated interactions of the drugs utilized by the patients. Interactions of important

severity were considered for presenting risk of life and/or demanding medical intervention to diminish or avoid serious adverse effects. The interactions involving medicinal plants were identified with the Manual of Phytotherapics of the National Association of Pharmacists (Anfarmag)[14].

Detection of PIM for elderly was conducted, based in Beers Criteria 2015[10], which consists in a list of drugs that were associated to negative outcomes to the elderly health, including confusion, falls and mortality.

It was created a database in the Microsoft Excel® 2007 for statistical analysis and it was applied descriptive statistical analysis for the quantitative variables through the program BioEstat (version 5.3). For the qualitative analysis it was used proportion.

The Institutional Review Board of the Institution where the trial was conducted approved the study, Report number and it was developed pursuant to the norms of Resolution 1.663.523 and was developed according to the standards defined in Resolution 466/12 of the Health National Council and by the Declaration of Helsinki of 2013. All the patients agreed and signed the Informed Consent Form.

RESULTS

Among the 20 study patients, males were predominant (70%), minimum age of 65 and maximum, 91 years old, mean of 73 years (SD = 7.9). Prostate cancer was the most common (25%), followed by breast and colon (20% each), multiple myeloma (15%), lung, rectum, bladder and lymphoma (5% each). The most reported comorbidities were systemic arterial hypertension (65%), *diabetes mellitus* and dyslipidemia (45%) and osteoporosis (25%), emphasizing that all the patients were affected by at least one and maximum four comorbidities.

It were detected 134 drugs (Chart 1) and 14 mineral supplements prescribed and/or utilized as self-medication, mean of 6.7 drugs per patient (SD = 2.5) of which, 41 (30.6%) were drugs destined to antineoplastic therapy and 93 (69.4%) to the treatment of diseases associated to the neoplasm or chronic infirmities developed earlier. The most used drugs were pantoprazole (9%), acid acetylsalicylic (9%), fluorouracil (9%), metoprolol (8%), simvastatin (8%), morphine (8%), acid zoledronic (8%) and omeprazole (2.2%). There were polymedicated 15 (75%) patients in use of five or more drugs (5 to 12).

It were identified 90 drug interactions, being 59 with different drugs in 16 (80%) patients, obtaining a median of four interactions/individual. According to the classification of severity of Micromedex®, 57 (63.3%) were identified as moderate, 20 (22.2%) as important and eight (8.8%) of mild severity (secondary). The drugs most involved in all the interactions classified were losartan and the association of sulfamethoxazole and trimethoprim (Bactrim®), followed by acid acetylsalicylic (AAS), morphine, mirtazapine, methadone, clonazepam, domperidone, simvastatin and fluorouracil.

The interactions encountered in Lexicomp® reached 85 and were classified according to the same classification of severity, being 54 (63.5%) moderate, 20 (24%) important and 11 (13%), mild. Of the interactions encountered in Lexicomp®, 40.6% were common to Drugs® and 19 (32.3%) to Micromedex Solutions®, 16 (27.1%) were common to the three databases.

Chart 1. Drugs utilized by 20 elderly according to the Anatomic Therapeutic Chemical Classification, 2019

Anatomic Group	Subgroup pharmacologic	Code*	Drug (n)	Subgroup pharmacologic	Code*	Drug (n)
Alimentary tract and metabolism	Peptic ulcer and gastroesophageal reflux	A02BC01	Omeprazole (3)	Mineral supplement	A12AX	Calcium (3)
		A02BC02	Pantoprazole (4)		A12AA03	Calcium gluconate (1)
	Antacid	A02AC01	Calcium carbonate (1)	Intestinal anti-inflammatory	A07EC02	Mesalazine (1)
	Antiemetic and anti-nausea	A04AA01	Ondansetron (1)	Glycemia reducers	A10BA02	Metformin (2)
					A10BK03	Empagliflozin (1)
	Insulin and analogues	A10AB05	Insulin aspart (1)		A10BB09	Gliclazide (2)
	Functional gastrointestinal	A03AX13	Simethicone (1)		A10BX02	Repaglinide (1)
		A03AA05	Trimebutine (1)		A10BH02	Vildagliptin (1)
	Propellers	A03FA01	Metoclopramide (1)		A10BB01	Glibenclamide (1)
		A03FA03	Domperidone (1)	Multivitamin combinations	A11AA03	Multivitamin (6)
Blood and hematopoietic organs	Antithrombotic agents	B01AC06	Acid acetylsalicylic (4)	-	-	-

Chart 1. continuation

Anatomic Group	Subgroup pharmacologic	Code*	Drug (n)	Subgroup pharmacologic	Code*	Drug (n)
Cardiovascular system	Antiadrenergic Agents	C02AC01	Clonidine (2)	Blockers or receptor of angiotensin II	C09CA01	Losartan (5)
	Diuretic	C03AA03	Hydrochlorothiazide (1)		C09CA03	Valsartan (2)
	Betablockers agents	C07AB07	Bisoprolol (1)		C09DB01	Valsartan + Amlodipine (2)
		C07AB02	Metoprolol (3)	Agents modifiers of lipids	C10AA07	Rosuvastatin (2)
		C07AB03	Atenolol (1)		C10AA01	Simvastatin (3)
	Agents acting in the smooth muscle	C02DB02	Hydralazine (1)	Angiotensin converting enzyme inhibitors	C09AA05	Ramipril (1)
					C09AA02	Enalapril (1)
	Stabilizers of capillary	C05CA53	Diosmin + hesperidin (1)	-	-	-
Musculoskeletal system	Affect the bone structure and mineralization	M05BA08	Acid zoledronic (3)	-	-	-
Respiratory system	Anti-histaminic of systemic use	R06AA02	Difenidramina (1)	Adrenergic inhalers	R03AK07	Formoterol + Budesonide (1)
	Inhalers	R03BB04	Tiotropium (1)	-	-	-
Anti-infection for systemic use	Antivirus of direct action	J05AB01	Acyclovir (2)	Sulfonamides and trimethoprim	J01EE01	Sulfamethoxazole + trimethoprim
Nervous system	Antiepileptic	N03AE01	Clonazepam (2)	Antidepressants	N06AX11	Mirtazapine (1)
		N03AX16	Pregabalin (1)	Anxiolytic	N05BA22	Cloxazolam (1)
	Antipsychotic	N05AX08	Risperidone (1)	Opioids	N02AA01	Morphine (3)
	Other analgesic and antipyretic	N02BB02	Dipyrone (2)	Additional disorders	N07BC02	Methadone (1)
	Antivertigo preparations	N07CA01	Betahistine (1)	-	-	-
Antineoplastic and immunomodulators agents	Hormones and related agents	L02BG03	Anastrozole (2)	Other antineoplastic agents	L01XC07	Bevacizumabe (2)
		L02AE03	Goserrelin (2)		L01XX32	Bortezomib (2)
		L02BX03	Abiraterone (2)		L01XC13	Pertuzumab (1)
		L02BA03	Fulvestrant (2)		L01XC03	Trastuzumabe (2)
		L02AE02	Leuprorelin (1)		L01XC02	Rituximab (1)
	Alkaloids and other natural products	L01CA05	Vinflunine (1)		L01XA03	Oxaliplatin (2)
		L01CD02	Docetaxel		L01XX19	Irinotecan (1)
	Antimetabolic	L01BA04	Pemetrexed (1)	Alkylating agents	L01AA01	Cyclophosphamide (1)
		L01BC02	Fluorouracil (4)	Immunostimulators	L03AA02	Filgrastim (1)
Sensorial organs	Preparation antiglaucoma	S01EE01	Latanoprost (1)	-	-	-
Hormone systemic preparations excluding sexual hormones	Corticosteroids	H02AB07	Prednisone (1)	-	-	-
Genitourinary system and sexual hormones	Drugs used in benign prostatic hyperplasia	G04CA52	Dutasteride + tamsulosin (1)	-	-	-
Various	Other therapeutic products	V03AF03	Calcium folinate (4)	-	-	-

Sources: Data of the author, according to the Anatomic Therapeutic Chemical Classification System (ATC).
Caption: *Code ATC.

The interactions followed the classification according to the mechanism of action: pharmacokinetic or pharmacodynamics. Of the interactions classified as "important", nine (45%) were characterized as pharmacokinetics (Table 1) and six (30%) as pharmacodynamics (Table 2). In these tables, the possible clinic effect, the mechanism and the recommendation are described.

About the interactions involving antineoplastic agents, five were encountered, either pharmacodynamic or pharmacokinetics (Table 3).

In relation to medicinal plants, it was reported the use by ten (50%) patients. The plants were: lemongrass (*Melissa officinalis*), chamomile (*Matricaria recutita L.*), Holy grass (*Cymbopogon citratus*) and green tea (*Camellia sinensis*) with lemon (*Citrus limón*). The presence of

possible interactions between drugs and medicinal plants was identified in four (20%) patients and consists in the use of chamomile with clopidogrel and AAS, whose result would be high risk of increasing the bleeding. The concomitant use of lemongrass and morphine presents risks by intensification of depressive action of CNS and green tea with valsartan by possible increase of the systemic arterial pressure[14].

After analysis of PIM for elderly, it was detected the use of seven different PIM and an exposure of 13 (65%) patients to at least one and maximum of three PIM (Table 4).

DISCUSSION

Polypharmacy can be considered a great problem in all age ranges, however, it represents major danger in elderly patients because of the elevate quantity of comorbidities, risks of drug interactions and side effects[15,16]. Added to this, the elderly presents physiologic alterations as, for instance, reduction of the gastric acidity, body water and serum albumin, increase in the percent of body fat, reduction of the volume of distribution of hydrosoluble drugs, increase of acid alpha glycoprotein, decrease of hepatic blood flow, among others that interfere in the metabolization of drugs and can negatively impact, predisposing adverse events[17].

Elderly present high prevalence of comorbidities that can influence the prognosis of cancer and tolerance to treatment[18]. Comorbidities as congestive heart failure, systemic arterial hypertension, dementia, depression, osteoporosis and chronic infections are frequently encountered in elderly oncologic patients[13]. These comorbidities were reported by the patients of this study.

Among the cases analyzed, there were two (10%) patients with excessive polypharmacy, they were in use of more than ten drugs. The frequency of polymedication (75%) encountered in this study is similar to what is described in the literature (40% to 84%)[19-22].

Table 1. Pharmacokinetic interactions of important severity encountered in the databases

Drugs	Clinic Effect	Mechanism	Recommendation
Hydrochlorothiazide + amlodipine + valsartan/ magnesium	↑*Toxic adverse effect of magnesium salts and hypotensive effect	Magnesium increases diuresis and additive effects of calcium reducers	Report signs of dizziness and tachycardia, xerostomia, weakness, crumps and increase fibers in the diet
Simvastatin/amlodipine	↑Serum concentration of simvastatin with risk of myopathy and rhabdomyolysis	Competition of substrates of both drugs by CYP3A4*	Limit the dose of statin to 20 mg/day
Domperidone/ sulfamethoxazole+ trimethoprim Domperidone/ondansetron Domperidone/bortezomib	↑QT interval prolongation*	Inhibition of CYP3A4 that potentializes the effect of domperidone	Avoid the combination and observe the patients for bradycardia and hypokalemia
Gliclazide/ vildagliptin	↑Hypoglycemic effect of sulfonylureas	Mechanism not elucidated	Reduce the dose of vildagliptin and monitor
Gliclazide/ aprepitant	↑Metabolism of CYP2C9*	Inducers of CYP2C9 increase the metabolism of the substrates of the same isoenzyme	Use of another antidiabetic or monitor
Clopidogrel/ morphine	↑*Concentração sérica de antiplaquetários	Delay of gastric emptying by the opioid elevates the time to reach the platelet maximum inhibition	Substitute for P2Y12*
Simvastatin/pantoprazole Simvastatin/omeprazole	↑Serum concentration of inhibitors HMG-CoA* reductase	Competitivity for CYP450*	Monitor the plasmatic concentrations of statins

Source: Lexicomp®, Micromedex®, Drugs®, 2017.
Captions: *CYP3A4: Cytochrome P450 3A4; Interval QT: Interval in the electrocardiogram between the beginning of the wave Q and the end of the wave T; CYP2C9: Cytochrome P450 2C9; P2Y12: Plate receptor; HMG-CoA:3-hydroxy-3methylglu-taryl-coenzime A; CYP 450: Cytochrome P450; ↓ reduction and ↑ increase.

Table 2. Pharmacodynamic interaction of important severity encountered in the databases

Drugs	Clinical effect	Mechanism	Recommendation
Methadone/clonazepam	↑*Depressive effect of CNS*: hypotension, profound sedation coma or death	Synergism	Avoid
Methadone /pregabalin Methadone /mirtazapin	↑Depressive effect of the CNS and risk of serotonergic syndrome	Synergism	Report the neuromuscular and mental alterations and diarrhea Avoid driving
Enalapril/losartan	↑Serum concentration and toxic effects of losartan: hyperkalemia, hypotension, kidney failure	Blockade of the system renin- angiotensin-aldosterone	Monitor electrolytes; Report symptoms of weakness and tingling of extremities
Glimepiride/ empaglifozin	↑Hypoglycemic effect	Synergism	Monitor or modify therapy
Morphine/risperidone	↑Depressive effect of CNS	Synergism	Monitor Avoid driving and operate machines

Source: Lexicomp®, Micromedex®, Drugs®, 2017.
Captions: *CNS: Central Nervous System; ↑ increase.

Table 3. Important severe pharmacodynamic and pharmacokinetics interaction involving immunomodulators/antineoplastic agents

Drugs	Clinical Effect	Mechanism	Recommendation
Fluorouracil/ Calcium folinate	↑Anticancer effects of fluorouracil Risk of anemia, diarrhea, granulocytopenia and thrombocytopenia	Calcium folinate stabilizes the complex 5-FU+FdUMP+TS- DNA*	Monitor symptoms of stomatitis, vomits, diarrheas and cutaneous reactions
Vinflunine/methadone	↑QT Interval prolongation*	Direct blockage of the potassium channels and cardiomyocytes injuries	Baseline electrocardiogram monitoring
Bevacizumabe/dipyrone	Dipyrone potentializes the myelosuppression toxic adverse effect and generates risk of agranulocytosis	Not clarified	Avoid
Hydrocortisone/ trastuzumabe	↑ Neutropenic effect	↑Bioavailability of corticosteroid	Monitor
Domperidone/bortezomib	↑QT Interval Prolongation	Inhibition of CYP3A4* that leads to the increase of the effect of domperidone	Avoid and observe patients for bradycardia and hypokalemia

Source: Lexicomp®, Micromedex®, Drugs®, 2017.
Captions: *Interval QT: Interval in the electrocardiogram between the beginning of the wave Q and the end of the wave T; 5-FU+FdUMP+TS-DNA: Fluorouracil + 5-fluoro-2′-deoxyuridine-5′-monophosphate + enzyme thymidylate synthase + acid deoxyribonucleic.

The prescription of multiple drugs can be necessary in some clinical situations, however, pharmacotherapy must be revised mainly in patients in oncologic treatment and can be indicated before the beginning of the treatment, or while changing the comorbidity management or in clinical condition determined by the multidisciplinary team during the care to the patient to prevent and detect adverse events as problems related to drugs and drugs interactions[13].

Patients with cancer utilize, in addition to antineoplastic, medications indicated to treat adverse events caused by them, as analgesics, antiemetic and vitamin supplements that can or not be associated to drugs indicated for other preexisting chronic diseases[23], situation

Table 4. Description of the potentially inappropriate medications for elderly utilized by the study patients

PIM	Risk	Recommendation
Clonazepam	Risk of cognitive impairment, *delirium*, falls, fractures and car accidents	Avoid
Clonidine	Bradycardia and orthostatic hypotension	Avoid
Omeprazole and pantoprazole	Infection by *Clostridium difficile*, bone loss and fracture	Avoid the use for more than 8 weeks except for patients in severe conditions with erosive esophagitis, pathologic hypersecretory condition in use of oral corticoids or NSAIDs*
Metoclopramide	Disorder of the late motor activity and extrapyramidal effects	Avoid, except in cases of gastroparesis
Difenidramina	Highly anticholinergic, reduction of clearance at advanced age, risk of confusion, dry mouth and constipation	Avoid
Glibenclamide	Prolonged hypoglycemia in older adults	Avoid

Source: *Beers Criteria*, 2015.
Captions: *NSAIDs: Non-steroidal anti-inflammatory; PIM: Potentially Inappropriate Medications.

observed in some diabetic and hypertense patients of this study. As polypharmacy identified among the patients was not analyzed qualitatively, it is not possible to affirm if all the mechanisms were actually necessary or not.

It is known that polypharmacy can be necessary in some situations as long as the patients are in treatment based in the best possible evidence available [9]. On the other hand, polypharmacy can become unnecessary because of the prescription in cascade and unbalanced medical care[24], generating prescriptions of multiple inappropriate medications where the benefit expected is not obtained[9].

In the study Health, Well-being and Ageing (SABE)[25], the risk of occurrence of drug interaction was 58% for those who received five drugs. When its use was greater or equal to seven, the risk raised to 82%. In the study of Alkan et al.[26], that included 445 elderly with cancer, approximately one third of the participants were exposed to PIM and drug interactions that were very severe[26]. In another study, that analyzed retrospectively the data of 244 patients with cancer and age greater or equal to 70 years, it were identified 769 potential drugs interactions in 75.4% of the patients[27]. This study detected 80% of the patients with possibility of suffering consequences of drug interactions.

The pharmacodynamic interactions are most affected by age and include great sensitiveness to agents that depress the Central Nervous System (as analgesic, opioids, hypnotic and sedative) and by the modification of the number or affinity of receptors. In this study, there were patients in use of methadone, morphine, cloxazolam, clonazepam, pregabalin and mirtazapine. In a same patient, the use of four drugs that cause respiratory depression and of the CNS (clonazepam, methadone, pregabalin and mirtazapine). A patient like this must be oriented to avoid risk actions that need mental agility and motor coordination and if feeling some exacerbated effect of the CNS, report to the doctor[28].

The safety and efficacy of a drug can be modified by the simultaneous exposure to several non-pharmaceutical products as dietary supplements and medicinal plants. These products usually based in popular knowledge are used frequently because of its low price, easy access and belief of inexistence of adverse reaction, which intensifies its indiscriminate consumption[11]. A prospective study, that evaluated the risk of drug interaction and interaction among plants and clinically relevant medications verified that, of the 149 patients with cancer in oncologic treatment, 84 reported the associated use of medicinal plants; for these individuals, it was observed a total of 122 possible interactions[29].

In relation to the PIM for elderly, in a study[30] with 500 elderly patients with cancer initiating treatment with chemotherapy, polypharmacy was verified in 48% and use of PIM in nearly 18% of the patients. In the analyzes of another study that included 1,595 patients with breast cancer and 1,528 patients with colorectal cancer, the frequency of PIM, based in the Beers Criteria[10], was of 22.2% and 24.8% in each group[31]. Feng et al.[32] identified among more than 45 thousand patients with breast cancer (n=17,630), prostate (n=18,271) and colorectal (n=9,420), the following rates of PIM respectively: 61.7%, 47.6% and 66.3%. In this study, it was found a general frequency of patients in use of PIM (65%) aligned with this last cohort study. It is interesting the use of lists of PIMs in clinical practice to avoid its use and inappropriate prescription. There are several lists as

Potentially Inappropriate Medications in the Elderly: The PRISCUS List[33], Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP)[34], List of Taiwan[35], European Union list of potentially inappropriate medications (EU (7)-PIM)[36], and the list of the Beers Criteria[10], which is the most utilized in the world[37]. To avoid the use of PIM and promote the rational use of drugs, there is a process of "deprescribing", that consists in the withdrawal of an inappropriate drug, supervised by a health professional with the objective of reducing polypharmacy and optimize the results[38]. Gradually, the scientific evidences indicate the effects of deprescribing, contributing for behavioral change and inclusion of deprescribing in the routine care of geriatric patients[39].

Among the positive aspects of the study, it stands out the possibility of detection of polypharmacy similar to what is described in the literature, the use of PIM and the possible drug interactions to alert the multiprofessional team about the risks and prevent them. As negative points, it is acknowledged that, when adopting the non-probabilistic sample by convenience, results that cannot be generalized are created, the sample is very reduced and is not representative; the non-realization of lab tests to follow up the results of the drug interactions, which hampered the association of polypharmacy with the negative outcomes.

CONCLUSION

Cancer treatment by itself is passible of charactering polypharmacy. In this report of multiple cases, it was detected among the elderly oncologic patients the occurrence of polymedication, potential drug interactions and use of PIM for elderly. This can indicate opportunity for the clinical pharmacist to act with oncologic patients. This professional can help to evaluate the risks and benefits of pharmacotherapy, encouraging the use of proper medications under correct conditions to treat diseases in the right manner.

CONTRIBUTIONS

All the authors contributed substantially for the conception and planning of the study, gathering analysis and interpretation of data and wording and/or critical review and final approval of the version published.

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DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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