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Profile of drugs for treatment of comorbidities in patients with cancer and associated levels of anxiety and depression

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Abstract: Managing cancer patients requires numerous drugs, such as chemotherapeutic agents and drugs for other chronic diseases. Thus, health teams must be aware of potential drug interactions that may be detrimental to health. This study analyzed the types of non-chemotherapeutic drugs used by cancer patients and screened patients undergoing cancer treatment for anxiety and depression. **Methods**: This cross-sectional study included 138 cancer patients receiving treatment at a reference center in Divinopolis, a city in the midwestern region of the state of Minas Gerais, from June to July 2014. Drug-related data were recorded in a form created by the authors, and the Hospital Anxiety and Depression Scale (HADS) was used for screening the patients for anxiety and depression. **Results**: Most patients (62.32%) were taking non-chemotherapeutic and chemotherapeutic agents. Eighty-nine types of drugs were reported. The most common drug classes were those that act on the cardiovascular and nervous systems, alimentary tract, and metabolism. Most patients were taking more than one drug, and 14 patients were taking 6 or more classes of drugs. The number of drug classes correlated with marital status and type of treatment. Anxiety and depression were found in 31.16% and 25.37% of the patients, respectively, and depression correlated with type of cancer ($p< 0.048$). **Conclusion**: The non-chemotherapeutic drugs taken by patients undergoing cancer treatment does not differ from those taken by the general population. Health professionals must bear in mind these patients' vulnerability to side effects and drug interactions, carefully assessing the risks and benefits of treatment and taking into account associated comorbidities, such as anxiety and depression.

Keywords*: Mental Health, Drug Incompatibility, Patient-Centered Care*

I. INTRODUCTION

Brazil is undergoing a demographic transition, namely, population ageing. Therefore, the prevalences of chronic health conditions tend to increase as they affect mainly older individuals [1]. A direct consequence of the growing prevalences of chronic diseases is the increased consumption of pharmaceutical drugs. Often individuals take more than one class of drugs, increasing the risk of drug interactions and adverse events, which are related to the number of drugs taken [2].

The management of patients undergoing cancer treatment requires numerous drugs, including chemotherapeutic agents, symptom-relieving drugs used for palliative purposes, and drugs for chronic diseases. Hence, health teams must be aware of possible drug interactions that may be detrimental to health and search for alternatives based on the best scientific evidence.

In this sense, knowing cancer patients' drug profile is critical as 30% of adverse events stem from the use of chemotherapeutic agents and their interactions with other drugs. The risk of drug interactions increases with the number of drugs being taken by the patient. Older adults are more susceptible to reactions, especially when they take multiple drugs to treat chronic diseases and have poor kidney and liver functions [3].

Drugs interact in many ways, two of which are pharmacodynamic and pharmacokinetic mechanisms. In a pharmacodynamic interaction two drugs have additive or antagonistic effects. On the other hand, pharmacokinetic effects occur when a drug interferes with the absorption and serum level of another drug, or the activation or inactivation of hepatic enzymes, which are responsible for the metabolism of many drugs. The cytochrome p450 system, a set of more than 50 enzymes responsible for stage I of metabolism, is one of the main systems affected by these interactions [3,4].

In addition to cancer and associated chronic diseases, individuals undergoing cancer treatment have a high prevalence of psychological and emotional disorders. Ten to thirty percent of cancer patients will have an

episode of major depression and/or anxiety during treatment [5]. Patients with chronic diseases exposed to polypharmacy also have a higher incidence of these disorders [6,7].

Given that patients undergoing cancer treatment may use more than one drug, requiring a thorough study of possible drug interactions, and the need of guaranteeing patients' safety, this study investigated the types of non-chemotherapeutic drugs used by cancer patients and screened patients undergoing cancer treatment for anxiety and depression.

II. METHODS

This cross-sectional study included 138 cancer patients receiving treatment at a reference center in Divinópolis, a city located in the midwestern region of the state of Minas Gerais, Brazil, from June to July 2014. The participants were selected based on medical record data. Patients without a diagnosis of cancer were excluded. The study was approved by the Human Research Ethics Committee of the Federal University of São João Del-Rei under protocol number 639.836/2014.

Patients who were receiving treatment at the time of data collection and who met the study profile were preselected to participate in the study. These patients were then approached randomly and invited to participate in the study. Patients who agreed to participate signed an informed consent form. The data collection instruments were previously tested on a group of 15 cancer patients by three trained individuals. Then study participants' data were collected on a daily basis during the study period.

The inclusion criteria were: a) being aware of the diagnosis; b) age equal to or above 18 years; c) receiving inpatient or outpatient treatment; d) having a cancer diagnosis (malignant tumor); and e) receiving treatment at the time of data collection. The exclusion criteria were: a) physiological inability to answer the questionnaire; and b) having a benign tumor diagnosis.

Two instruments collected were used for data collection, a sociodemographic and clinical form and the Hospital Anxiety and Depression Scale (HADS). The form, created by the authors, helped to screen outpatients and inpatients. The data were then obtained from the patients' medical records. The study variables were: sex, age, treatment duration, cancer location, type of treatment, education level, and drug regimen. The drugs were classified according to the Anatomical Therapeutic Chemical Classification (ATC) [8].

The second instrument is the HADS, developed by North American researchers for use in hospitals; it has been validated in Brazil and does not require authorization for use [9,10]. HADS is a self-administered scale, which may be read out loud for illiterates or people with disabilities. It consists of closed questions that screen for depression and/or anxiety based on how the person felt in the last week. HADS does not investigate physical symptoms, such as dizziness, headache, insomnia, and fatigue, or symptoms related to mental disorders. The absence of these variables prevents somatic disorders from compromising the final score, avoiding detection bias [9].

The participants' profiles were descriptively analyzed, and the data were tested by the Pearson's chi-square test using the biostatistics software Epi Info 7.0. The analysis was based on epidemiological elements, and the results were presented in figures.

III. RESULTS

The sample consisted of 138 patients, 69.57% females and 30.43% males. Most were outpatients (79.71%). The patients were approached in the chemotherapy room (65%) in the waiting room for radiotherapy (20%), or in the ward (15%).

Most patients were aged 49 to 58 years. The mean age ± standard deviation (SD) was 58 ± 16.08 years. Most patients were married (65%), 41% had not completed elementary school, and 28.9% had completed high school.

The most common cancers in males were: prostate (16.6%), colorectal (16.6%), esophageal (11.9%), larynx (11.9%), and lung (7.14%). In females the most common cancers were: breast (61.4%), ovarian (8.3%), colorectal (6.25%), and lung (5.2%).

Most patients (71.01%) were undergoing chemotherapy, 15.22% were undergoing chemotherapy and radiotherapy, 9.42% were undergoing radiotherapy, and 4.35% were waiting for surgery.

The time elapsed between diagnosis and the interview varied from 6 months to 3 years in 48.55% of the participants. Some patients (34.78%) had fewer than 6 months of treatment, and 8.70% had 5 to 10 years of treatment.

Table 1 shows the primary organs affected by cancer.

Table 1 – Main cancer sites in 138 patients receiving cancer treatment at a reference hospital.

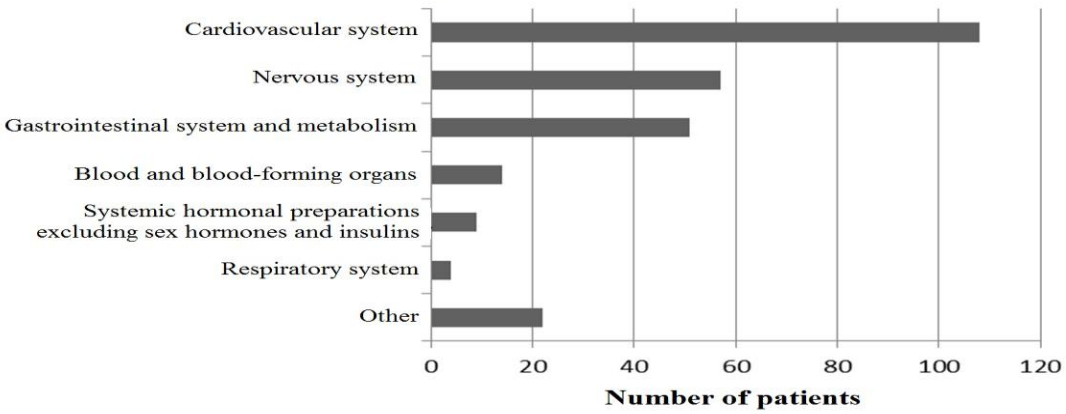
Characteristics	N
Types of cancer:	
Breast	60
Colorectal	13
Esophageal	8
Ovarian	8
Lung	8
Prostate	7
Stomach	6
Larynx	6
Leukemia	4
Pancreas	3
Cervical	2
Testicular	2
Non-Hodgkin lymphoma	2
Oral	1
Hodgkin lymphoma	1
Skin – nonmelanoma	1
Other	6
Total	138

Most patients (62.32%) were taking chemotherapeutic and non-chemotherapeutic drugs, and 37.68% were not taking any drug. The patients were taking 89 different types of drugs to treat conditions other than cancer, as follows: losartana (14.5%); metformin (10.9%); sinvastatin and omeprazol (9.4%); clonazepam, hydrochlorothiazide, and atenolol (8.7%).

Additionally, most patients were taking more than one drug as follows: 10.1% used six or more classes of drugs; 5.80% used five classes; 5.07% used four classes; 11.59% used three classes; 13.04% used two classes; and 16.67% used only one class.

Graph 1 shows the main targets of the non-chemotherapeutic drugs.

Graph 1: Main Sites of Drug Action in Cancer Patients according to the Anatomic Therapeutic Chemical Classification



Drugs that act on the cardiovascular system prevail, probably for the treatment of high blood pressure, which may constitute a comorbidity.

Table 2 shows the main classes of drugs being taken by the participants. Such classes cover the main targets of public health campaigns, such as high blood pressure and diabetes mellitus.

Table 2: Main classes* of drugs used by 138 patients receiving cancer treatment at a reference hospital in the midwestern region of Minas Gerais. MG. Divinópolis, 2014.

Drug		
C Cardiovascular system		N
C09	Agents acting on the renin-angiotensin system	36
C03	Diurectics	24
C07	Beta blocking agents	22
C10	Lipid-lowering drugs	15
C01	Cardiac therapy	4
C08	Calcium channel blockers	7
N Nervous system		
N06	Psychoanaleptics	16
N05	Psycholeptics	25
N02	Analgesics	9
N03	Antiepileptics	7
A Alimentary tract and metabolism		
A10	Drugs used in diabetes	29
A02	Drugs for acid-related disorders	14
A03	Drugs for functional gastrointestinal disorders	5
A04	Antiemetics and antinauseants	6
B Blood and blood-forming organs		
B01	Antithrombotic agents	12
B03	Antianemic preparations	2
H Systemic hormonal preparations excluding sex hormones and insulins		
H03	Thyroid therapy	5
H02	Corticosteroids for systemic use	4
R Respiratory system		
R03	Drugs for obstructive airway diseases	4
Others		22

*Classification established by the Anatomical Therapeutic Chemical Classification

Table 3 shows the sociodemographic and clinical characteristics of the participants, and the number of drug classes they use, correlating the sociodemographic characteristics with possible candidates for polypharmacy.

Table 3: Correlation between the sociodemographic and clinical characteristics and the number of drug classes used by cancer patients.

Number of classes		1	2	3	4	5	6	None	Total	p-value
Sex:	Female	18	10	11	6	5	8	38	96	0.560
	Male	5	8	5	1	3	6	14	42	
Age:	18 to 28 years	1	0	0	0	0	0	3	4	0.149
	29 to 38 years	1	2	1	0	0	0	9	13	
	39 to 48 years	8	2	3	3	0	1	12	29	
	49 to 48 years	5	6	6	2	2	1	15	37	
	59 to 68 years	5	5	3	1	3	9	7	33	
	More than 68 years	3	3	3	1	3	3	6	22	
Marital status:	Married	11	15	11	5	6	8	34	90	0.005
	Single	6	0	3	1	1	0	13	24	
	Divorced	5	1	0	0	1	1	5	13	
	Widowed	1	2	2	1	0	5	0	11	
Education level:	Incomplete elementary school	10	5	6	4	4	6	22	57	0.367
	Complete elementary school	2	4	2	2	1	1	3	15	

	Incomplete high school	1	1	1	0	0	1	3	7	
	Complete high school	5	6	3	1	3	3	19	40	
	Incomplete higher education	1	1	0	0	0	1	4	7	
	Complete higher education	4	0	3	0	0	0	0	7	
	Illiterate	0	1	1	0	0	2	1	5	
Type of treatment:	Radiotherapy	1	1	1	0	3	4	3	13	0.013
	Surgery	0	3	0	0	0	1	2	6	
	Chemo+Radiotherapy	6	1	5	0	0	2	7	21	
Type of cancer:	Oral	1	0	0	0	0	0	0	1	0.790
	Colorectal	2	1	1	1	1	2	5	13	
	Cervical	1	0	0	0	0	0	1	2	
	Esophageal	1	1	0	0	0	2	4	8	
	Stomach	0	3	0	0	0	0	3	6	
	Larynx	1	0	1	0	1	0	3	6	
	Leukemia	0	1	0	0	0	3	0	4	
	Hodgkin lymphoma	0	0	1	0	0	0	0	1	
	Non-Hodgkin lymphoma	0	0	0	0	0	1	1	2	
	Breast	10	6	9	3	4	4	24	60	
	Ovary	2	1	1	0	1	0	3	8	
	Pancreas	2	1	0	0	0	0	0	3	
	Skin, non-melanoma	0	0	0	0	0	0	1	1	
	Prostate	1	1	1	1	1	1	1	7	
	Testicular	0	0	0	0	0	0	2	2	
	Others	0	2	1	1	0	0	2	6	
	TOTAL	23	18	16	7	8	14	52	138	

Ninety-five (68.84%) patients scored between 0 at 7 points in the HADS, indicating that they probably did not have anxiety; 30 (21.74%) patients scored between 8 and 11 points, indicating that they probably had anxiety; and 13 (9.42%) patients scored between 12 and 21 points. The mean score was 5.68 ± 4.03 points. The estimated prevalence of anxiety was 31.16%.

One hundred and three (74.64%) patients scored between 0 and 7 points for depression; 23 (16.67%) patients scored between 8 and 11 points; and 12 (8.70%) patients scored between 12 and 21 points. The mean score for depression was 4.91 ± 4.19. Therefore, the estimated prevalence of depression was 25.37%.

Table 3 shows that the only sociodemographic variable correlated with the number of drug classes was marital status ($p<0.005$). Regarding HADS, depression correlated with type of cancer ($p<0.048$).

IV. DISCUSSION

The study prevalence of non-chemotherapeutic drugs was 62.32%, in agreement with the literature[16].

Participant characterization showed that young adults are developing cancer. Most participants were women at the end of their childbearing years, leading one to wonder whether they had been informed about screening tests, especially breast self-exam, and whether they had had mammograms, given that breast cancer was the most frequent type of cancer in this group. All breast exams are offered by the Unified Healthcare System, so other studies should try to clarify these doubts.

The variables marital status and type of treatment were associated with the number of drug classes used by the participants. These results disagree with the literature, since other authors have reported that polypharmacy was associated with gender, education level, and frequency of seeking health services [11]; and with perceived health, presence of chronic diseases, and having private health insurance [16].

Regarding the association between marital status and number of drug classes used, widowed patients were using at least one drug, and 45% of them were using six drugs or more. Similar results have been reported by other studies [22], namely the use of drugs by older adults in the general population and the significant relationship between the use of various drugs and marital status, especially widower-/widowhood.

The literature shows an association between advanced age and polypharmacy, which is justified by the various chronic diseases that affect this population and shows the importance of interdisciplinary cooperation, especially for the treatment of vulnerable groups, like older individuals [17].

The study showed that most cancer patients use long-term non-chemotherapeutic drugs, requiring health professionals to use caution when prescribing and administrating drugs, and to be mindful of drug interactions and adverse effects in order to manage patients safely.

The variety of drug classes used by cancer patients is noteworthy as many drug classes are unrelated to cancer. Thus, health professionals need to identify other diseases that may be present in this population in

addition to cancer-related problems, including complications of various causes, such as those related to the cardiovascular and central nervous systems. Polypharmacy stems from treating many diseases and symptoms, such as high blood pressure, diabetes, insomnia, and depression, among many others [7,11].

The main class of drugs used by the study participants is for the cardiovascular system, especially antihypertensives and dyslipidemics. These diseases have high prevalences in the general population, so they expectedly prevail in cancer patients too. The World Health Organization (WHO) estimates that one-third of adults globally have high blood pressure, and its prevalence tends to increase with age [12,13]. The rate of self-reported dyslipidemia in the general population is 16.5%, representing a major public health problem [14].

Cardiovascular and chemotherapeutic drugs may interact. Renin-angiotensin system blockers may block the synthesis of erythropoietin and exacerbate anemia, while beta blockers and calcium channel blockers, like most statins, are substrates of hepatic enzymes [15], so they may increase the toxicity of chemotherapeutic agents and their effects [3].

Regarding drugs for the central nervous system, many study participants were taking antidepressants and anxiolytics. Cancer patients have a higher prevalence of anxiety and depression than the general population [5], but these conditions are even more prevalent in individuals with multiple chronic diseases [11]. Thus, the use of drugs for psychiatric disorders by cancer patients was expectedly widespread.

Health professionals must remain alert for the possibility of adverse events. Since most drugs used by these patients are metabolized by the liver, interactions between chemotherapeutic and psychoactive agents may occur [3].

Blood glucose-lowering drugs are the most common metabolism-related drugs taken by the study group. In Brazil the prevalence of diabetes mellitus (DM) in individuals aged 30-69 years is 7.6%, representing almost 10 million people. The age group affected by DM concentrates most of the cancer patients, so some study patients expectedly have DM [6].

Some study participants were also taking symptom-relieving drugs, such as analgesics and antiemetic agents, but the use of these drugs related to the use of chemotherapeutic drugs. Vomiting and nausea are common side effects of many chemotherapeutic drugs, and since many cancers cause pain, chronic use of analgesics was common.

Antiemetics, like ondasetron, interact with many drugs, including chemotherapeutic agents, so the former may reduce the effectiveness of the latter. On the other hand, opioid analgesics delay intestinal transit. A change in drug absorption rate may reduce its efficacy. Nonsteroidal anti-inflammatory drugs (NSAIDs) prevent platelet aggregation and may lead to bleeding, especially when associated with anticoagulants or in the presence of thrombocytopenia. Additionally, the use of NSAIDs may reduce renal flow and increase the toxicity of some chemotherapeutic agents, such as methotrexate [3].

Type of treatment was related with the number of drug classes used by the study patients. Cancer patients undergoing chemotherapy do require an increasing number of drugs [18]. First, the cancer diagnosis by itself is associated with an increased use of drugs. Then there are the adverse effects caused by the cancer treatment. For example, chemotherapy, the most common treatment used by the study group, is highly toxic. Additionally, sometimes the long-term use of certain drugs is needed to control the side effects of chemotherapeutic agents, justifying the relationship between type of treatment and number of drug classes [19,20,21].

Anxiety and depression did not correlate with the use of various drug classes by the study participants. According to HADS, the prevalences of anxiety and depression were 29.82% and 27.06%, respectively. These findings corroborate the literature, since cancer patients expectedly have prevalences of anxiety and depression of 30% and 22%, respectively [23].

The levels of anxiety and depression did not correlate with the study variables. These findings disagree with the literature, which lists female and young patients as risk groups for anxiety. Moreover, anxiety is inversely correlated with socioeconomic level and education level [24,25]. On the other hand, depression is classically related to being female, being aged 20 to 40 years, having low income and education level, being divorced, separated, or widowed, living alone, and lacking social support [26], which was also not confirmed by the present study, probably because of the small sample size. Anxiety is more frequent in patients with a recent cancer diagnosis, and depression, in patients without possibility of treatment [5].

Type of cancer was significantly associated with depression, especially breast cancer as 25% of the breast cancer patients were positive for depression. This finding is corroborated by the literature [15], which reports that the three cancers with the highest prevalences of psychiatric comorbidities are breast cancer (30%), pancreatic cancer (21%), and oropharyngeal cancer (10.5%). Additionally, breast cancer is classically associated with psychiatric disorders since its diagnosis and treatment greatly impact a woman's sex life, self-image, and self-esteem [22].

The present study has some limitations. First, the sample size is small and the study was conducted in a single healthcare facility. Second, most patients were females with breast cancer, which can limit the study applicability. Finally, the study did not investigate side effects, adverse events, and especially, drug interactions.

V. CONCLUSION

Analysis of the types of non-chemotherapeutic agents used by cancer patients showed that the drugs they take for other chronic diseases does not differ from those taken by the general population. The most prevalent drug classes are those that act on the cardiovascular system, followed by those that act on the central nervous system, alimentary tract, and metabolism.

The use of various classes of drugs is common in this population, especially in widowed individuals and those undergoing chemotherapy. Additionally, disorders such as anxiety and depression are more common in cancer patients and related to the type of cancer.

In this context, health professionals should bear in mind the possible occurrence of side effects caused by drug interactions and adopt safe management. This is a challenge for oncologists given the incidence of cancer-related comorbidities.

The risks and benefits of different types of treatment should be assessed by a multidisciplinary team.

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