





## Profile of patients with hematological toxicity grades 3 and 4 and gastrointestinal toxicity of patients undergoing chemotherapy

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### ABSTRACT

The administration of chemotherapeutic agents may lead to the occurrence of toxicities in organic systems not affected by cancer. This study aimed to evaluate the profile of patients with hematological toxicity grades 3 and 4 and gastrointestinal toxicity of patients undergoing chemotherapy. There was a prevalence of 48.70% of gastrointestinal toxicity, 42.20% of hematological toxicity and 9.10% of hematological and gastrointestinal toxicities. The most common symptoms of toxicity grade 3 was Hb <8.0 - 6,5g/dl (47.05%), and of hematological toxicity grade 4 was febrile neutropenia (44.44%). Patients with gastrointestinal toxicity presented vomiting (43.69%), diarrhea (21.84%) and nausea (20.16%). There was an association between the development of toxicities and the variables purpose of chemotherapy, modality of treatment, type of cancer staging and smoking. Knowing the profile of these patients may help the nurse in the early identification of symptoms for adoption of clinical protocols aimed at minimizing the symptoms and improving the patient's coping process of the treatment.

**Keywords:** Chemotherapy; Prevalence; Side effects and adverse reactions related to medications; Toxicity; Pharmacosurveillance

### 1 INTRODUCTION

According to the report "World cancer report 2014" of the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), the

cancer is a public health problem, with over 18 million cases in 2018, and estimated 29 million cases for 2040 (WHO, 2019). For the triennium 2020-2022, the expected incidence is of 625 thousand new cases of cancer in Brazil, and may reach 685 thousand new cases, when considering the unreported cases. Except for non-melanoma skin cancer, there will be other 450 thousand cases of the disease (INCA, 2019).

The advances in the diagnosis and treatment of cancer has allowed an increase in survival in an increasing number of people with oncological diseases, in part due to early detection, a broader selection of treatment options, as well as a better clinical management of the disease (BONASSA, 2012).

The oncologic treatment options include surgery, hormone therapy, immunotherapy, targeted therapy, bone marrow transplant, radiotherapy, palliative care and chemotherapy. The chemotherapeutic treatment is one of the therapeutic modalities most often used in clinical practice for cancer control, and consists of using isolated or combined chemical substances to treat malignant neoplasms, acting directly on the growth and division of cells (BONASSA, 2005).

According to the purpose, chemotherapy can be classified into curative, palliative, neoadjuvant and adjuvant. The curative chemotherapy aims to achieve the complete control of the tumor. The curative palliative has no curative purpose, and is indicated to improve the quality of patient survival. The neoadjuvant type is indicated to obtain partial reduction of the tumor, aiming at a complementary treatment with surgery and/or radiotherapy, while the adjuvant chemotherapy is used after curative surgery aiming to sterilize local or circulating residual neoplastic cells. The choice of the type of chemotherapy to be used will depend on the degree of malignancy, the tumor type and the general involvement of the patient (INCA, 2018).

The most common agents used in the treatment of cancer include the polyfunctional alkylating agents, antimetabolites, antitumor antibiotics, mitotic

inhibitors, among others, which act in a specific or nonspecific manner in different phases of the cell cycle, causing damage to DNA and cell death (INCA, 2018). However, although the chemotherapy treatment destroy tumor cells, the antineoplastic drugs also affect normal cells, especially those with fast reproduction. The aggressiveness of the chemotherapeutic agent to cells focuses particularly on the bone marrow, germinal tissue, hair follicle and gastrointestinal tract, causing systemic changes in the patient under treatment. All of these changes, present in greater or lesser degree, predispose the patient to several complications, reducing the quality of life and survival (BONASSA, 2005; RIUL; AGUILAR, 1999).

In relation to the degree of toxicity, the National Cancer Institute of the United States (NCI) published in 2010, the 4<sup>th</sup> volume of the Common Terminology Criteria for Adverse Events (CTCAE). It is a descriptive terminology of toxicity of chemotherapeutic agents, accompanied by a severity scale (grades 0 to 5), according to the organic systems involved (BERTOLAZZI *et al*, 2015). In this way, the grades of toxicity of chemotherapeutic agents are defined as: Grade 0: no occurrence of adverse event or within normal values; Grade 1: mild, without medical intervention, asymptomatic and only detected on radiographic or laboratory findings; Grade 2: Moderate, with minimal intervention, local or non-invasive intervention; Grade 3: severe and undesirable, significant symptoms that require hospitalization or invasive intervention, blood transfusion, radiological intervention, elective surgery; Grade 4: life-threatening or incapacitating, with physiological consequences that need intensive care or emergency invasive procedures; Grade 5: death (BONASSA; 2012).

Among the most common adverse effects of chemotherapy treatment, there stand out gastrointestinal and hematological toxicities, whose most frequent symptoms are nausea and vomiting, mucositis, myelotoxicity, among others (CAVALER *et al*; 2017).

Nausea and vomiting has a very large impact on the quality of life of patients, as well as in their nutritional status, thus being important to prevent it. From the

advances of researches in the area of oncology in recent years, the nausea and vomiting resulting from chemotherapy treatment had a better control, through the antiemetic therapy, especially for acute nausea and vomiting (CAVALER *et al*; 2017). The early identification of nausea and vomiting associated with chemotherapy is important for early intervention and improvement of clinical conditions for the patient's coping process of the treatment.

Almost all chemotherapeutic agents exert toxicity on the formation of hematopoietic tissue, thus called myelosuppressor or myelotoxic, and this is the most important toxicity related to the use of these drugs (ÁVILA; SOARES; SILVA, 2013). A literature review identified that, some of the most cited toxicities in the literature are the neutropenia (31%), cardiotoxicity (23%), infection (23%) and mucositis (23%) (IUCHNO; CARVALHO, 2019). Another study shows higher percentages of hematological toxicity than those of gastrointestinal toxicity. The main symptoms of these toxicities are the neutropenia (41%) and thrombocytopenia (6%), and nausea and vomiting (21%) (ROQUE; FORONES, 2011).

The occurrence of hematological and gastrointestinal toxicities can bring consequences to the chemotherapy treatment. According to Roque and Forones (2011), 47% of patients on chemotherapy experience toxicities, and 76% of those need reduction of doses and 11% cease the therapy. A study conducted by Barbosa (2018) describes that 60% of the patients presented delays between cycles and weeks of treatment. In 50% of the cases, there was reduction of doses between cycles and weeks of treatment, and in 33.3%, suspension of treatment due to the occurrence of hematological toxicity. The study reported 67 delays, with an average of 5.02 days, due to symptoms related to the occurrence of hematological and gastrointestinal toxicities. Concerning the reduction between weeks of chemotherapy, there was a reduction of doses in 24.8% of weeks of treatment, and of these, 39.7% were due to symptoms of hematological toxicity (ROQUE; FORONES, 2011).

The toxicity of chemotherapeutic agents is frequently considered as a limiting factor for dosage and fractionation of drugs, since its worsening may cause irreversible or lethal damage to the patient. Therefore, the planning of the patient's care should consider factors such as age, nutritional status, renal, liver and lung function, type and location of the tumor, presence of metastases and its extension (RIUL; AGUILAR, 1999).

Therefore, it is important to understand the possible reactions presented by the patient on chemotherapy treatment, in particular the signs of hematological and gastrointestinal toxicities, and seek the possibilities of prevention or treatment in a timely manner, since the absence of these actions will increase the chances of occurrence of cases of complications of these toxicities, which can lead to changes in the programmed therapeutic plan or interruption in treatment (BERTOLAZZI *et al*, 2015).

Regarding the care with cancer patients, the nurse oncologist is responsible for planning, implementing and evaluating the care provided to patients, according to the type of neoplasm or therapeutic protocol, through evidence-based practice and implementation of protocols described and implemented in the institution. Thus, Nursing has a fundamental role in the evaluation and control of the signs and symptoms of toxicity related to chemotherapy, manifested before, during and after the administration of antineoplastic agents. The correct and timely identification of symptoms of toxicity resulting from chemotherapy treatment, in particular those of hematological and gastrointestinal toxicity, enables the implementation of actions essential for the clinical management of the patient, avoiding serious and undesirable outcomes such as death or cardiac arrest, depending on the grade of toxicity (FONSECA, 2013; CAVALER, 2017).

During the clinical practice of nurses oncologists from a reference center for cancer treatment in the Zona da Mata in Minas Gerais, in the Emergency Care, the visits were mostly from patients with complications from chemotherapy treatment, and with signs and symptoms such as nausea, vomiting and fever, which can arise

from hematological and gastrointestinal toxicities of the chemotherapy treatment in progress. Although the hospital is a center of excellence in chemotherapy treatment, there are no studies conducted in this site to identify the prevalence of occurrence of hematological toxicity grades 3 and 4 and gastrointestinal toxicity in patients undergoing outpatient and inpatient chemotherapy.

Thus, this study was outlined with the objective to evaluate the profile of patients with hematological toxicity grades 3 and 4 and gastrointestinal toxicity in patients on chemotherapy in a hospital of oncological treatment, as well as the variables associated with the occurrence of these toxicities. Knowing the profile of these patients is important for the construction and deployment of prevention protocols focused on these toxicities, in order to individualize the care, allowing the prevention or minimization of the treatment effects, in order to avoid hospitalizations or interruptions of chemotherapy sessions due to patient's clinical worsening.

## **2 MATERIAL AND METHOD**

This is a cross-sectional study, conducted in the emergency care of an oncological hospital in the Zona da Mata in Minas Gerais. The same is maintained by resources generated by the services provided, with 92% of assistance to the UHS, in addition to grants and public resources. It is considered mid-sized, with 170 beds and six active surgical rooms. It provides services at outpatient level, such as chemotherapy, radiotherapy, and presents wide structure of offices, in addition to various diagnosis-supporting services.

The study population comprised all patients treated in the emergency care in the period of data collection, totaling 793 patients. The sample size calculation was performed on OpenEpi program version 3.01, considering a confidence interval of 99%, and a prevalence of hematological toxicity of 7.69%, and gastrointestinal toxicity of 8%. This prevalence was estimated with the completion of a pilot study, which evaluated the occurrence of these outcomes in the

population studied during 60 days. Thus, the minimum required sample for the study was 153 patients. However, the final sample of the study comprised 154 patients, thus extrapolating minimum sample necessary for accomplishing the study.

There was inclusion of the medical records of patients treated in the emergency department of the institution, aged over 18 years, with cancer of different etiologies, undergoing chemotherapy treatment, at any stage of treatment, in the outpatient and inpatient infusion regimens, experiencing the signs and symptoms related to the hematological toxicities grades 3 and/or 4, and/or gastrointestinal toxicities. The study did not include patients treated in the emergency care that had not been submitted to chemotherapy in the hospital, and who had no signs and symptoms related to the hematological toxicity grades 3 and/or 4, and/or gastrointestinal toxicity.

Data collection was carried out in the period from August to October 2019, through the analysis of medical records of patients admitted to the Emergency Department of the hospital under study, and that met the aforementioned inclusion criteria. For the construction of the data collection instrument, there was a search for articles related to the theme using the descriptors “chemotherapy”, “prevalence”, “side effects and adverse reactions related to medications”, “adverse reaction”, “toxicity”, “pharmacosurveillance” and “adverse effect” on databases LILACS, PUBMED, Cochrane, Scielo, Capes Journals and Cinahl. The publications selected discussed the prevalence and factors associated with the occurrence of gastrointestinal toxicity and hematological toxicity grades 3 and 4. Thus, the variables of interest in the study were listed. Once built, the pilot test was performed with the application of the data collection instrument to a sample of 20 records. After review of layout and organization of the arrangement of items, the data collection instrument was finalized.

The dependent variables in the study were hematological toxicity grade 3, grade 4 and gastrointestinal toxicity. Hematological toxicity grade 3 is a severe event or, from a medical point of view, something that does not represent a significant risk to life. Indicated hospitalization or its prolongation; incapacitation,

limitation of the self-care in everyday activities, such as bathing, dressing, undressing, eating, using the bathroom, taking medications (CTCAE,2011). These are: Anemia: Hb <8,0-6.5 g/dl (blood transfusion indicated), Neutropenia: absolute neutrophil counts <1000-500/ $\mu$ l, febrile neutropenia: absolute neutrophil counts <1000 lymphocytes/ $\mu$ l and a temperature measurement >38.3°C or sustained temperature by more than 1 h  $\geq$  38°C, thrombocytopenia, platelet <50.000-25.000/ $\mu$ l (MOURA, 2017).

The hematological toxicity grade 4 is defined as an event with life-threatening consequences, indication for urgent intervention (CTCAE,2011). These are: Anemia: Hb <6.5 g/dl, Neutropenia: absolute neutrophil counts <500/ $\mu$ l, Febrile Neutropenia: life threatening condition, Thrombocytopenia, platelet <25,000/ $\mu$ l (MOURA, 2017).

Gastrointestinal toxicity was defined as a severe event or, from a medical point of view, something that does not represent a significant risk to life. Indicated hospitalization or its prolongation; incapacitation, limitation of the self-care in everyday activities, such as bathing, dressing, undressing, eating, using the bathroom, taking medications (CTCAE,2011). These are: nausea: inadequate intake of fluids or high caloric foods, with indicated hospitalization, enteral and/or parenteral nutrition. Vomiting: 6 or more episodes (separated by 5 min in 24 hours; indicated hospitalization, enteral and/or parenteral nutrition. Mucositis: severe pain that interferes with oral ingestion. Anorexia and cachexia: Important weight loss or malnutrition (inadequate caloric intake), indicated enteral and/or parenteral nutrition. Diarrhea: 7 or more bowel movements a day, incontinence, limitation of physical activities of daily life. Constipation: obstipation with indication of manual evacuation, limitation of personal care and activities of daily life (MOURA, 2017).

The independent variables of the study were sex, schooling, family income, age, city of origin, weight, height, body mass index, comorbidities, use of alcohol, use of cigarettes, drugs of continuous use, need for hospitalization, type of cancer on treatment, staging of the disease, type of chemotherapy protocol, chemotherapy purpose, treatment modality, mode of administration of the



chemotherapeutic agent, number of cycles performed, the day of the cycle that sought care.

The data were organized on a spreadsheet in Excel® and the descriptive measures were calculated through descriptive statistics with an analysis of the distribution of frequency. To evaluate the association between the variables sex, weight, height, body mass index, co-morbidities, type of chemotherapy protocol used, chemotherapy purpose and the outcomes of the study, the chi-square test was performed to examine whether there was a difference of proportion in the occurrence of outcomes between the groups, considering a confidence interval of 95%. Data analysis used the statistical program SPSS version 23.0.

This study complied with the ethical precepts of Resolution 466/2012 of the National Health Council on researches involving human beings, being approved by the Research Ethics Committee of the University through Opinion n. 3.077.130. Since this is a documental research, whose data were collected from patients' medical records, there was no need for the Informed Consent Form.

### **3 RESULTS**

The sociodemographic profile, health conditions and life habits, history of the current disease and chemotherapy treatment carried out were analyzed, as well as the occurrence of hematological and gastrointestinal toxicities.

In relation to the sociodemographic profile, most patients (148 - 96.10%) were from the Zona da Mata in Minas Gerais, followed by patients from Vale do Rio Doce (4 - 2.59%). In addition to Minas Gerais, there were patients from the states of Rio de Janeiro (1 - 0.64%), and Espírito Santo (1 - 0.64%), which belong to the regions of care covered by the health institution. The mean age of the patients was 56 years (+15 years; 18-87 years; Mode: 47 years).

Table 1 shows the data related to other variables investigated to trace the sociodemographic profile of the studied patients.

Table 1 – Sociodemographic profile of the surveyed patients – Muriaé – Minas Gerais – Brazil – 2019

<b>Variable</b>	<b>N</b>	<b>%</b>
<b>Sex</b>		
Female	85	55.20
Male	69	44.80
<b>Profession</b>		
Housekeeper	30	19.50
Rural worker	28	18.18
Teacher	11	7.14
Other	80	51.94
Uninformed	5	3.24
<b>Education</b>		
Incomplete elementary school	59	38.35
Complete elementary school	40	25.97
Complete high school	26	16.88
Complete higher education	11	7.14
Illiterate	7	4.54
Uninformed	5	3.24
Incomplete high school	4	2.59
Uninformed	2	1.29
<b>Income</b>		
Up to 1 minimum wage	35	22.75
2 - 3 minimum wages	34	22.07
Over 3 minimum wages	33	21.42
1 - 2 minimum wages	30	19.48
Uninformed	22	14.28
<b>Total</b>	<b>154</b>	<b>100</b>

Source: Authors (2020)

In were: Patient's medical record

The analysis of Table 1 allows inferring that the most (85 - 55.20%) of the patients admitted to the emergency care in the period of the study development were female, had complete elementary education (78 - 67.28%). The majority (58 -

37.68) is housekeeper and rural workers, and have an income of up to 3 minimum wages (99 - 64.30%).

The health conditions and life habits of the patients were analyzed at data collection (Table 2).

Table 2 - Health conditions and life habits of the surveyed patients - Muriaé - Minas Gerais - Brazil - 2019

Variable	N	%
<b>Body Mass Index (BMI)</b>		
Adequate weight: BMI $\geq 18.5$ e $< 25$	85	54.55
Overweight: BMI $\geq 25$ e $< 30$	30	19.48
Underweight: BMI $< 18.5$	27	17.53
Obesity: BMI $\geq 30$	13	8.44
<b>Co-morbidities</b>		
None	81	52.61
Hypertension	60	38.96
Diabetes	3	1.94
Other	10	6.49
<b>Continuous use of medications</b>		
Yes	127	82.48
No	26	16.88
Uninformed	1	0.64
<b>Smoking</b>		
Never quit	110	71.45
Quit smoking	31	20.12
Active smoker	12	7.79
Uninformed	1	0.64
<b>Alcohol consumption</b>		
Never drank	95	61.70
Quit drinking	41	26.62
Active alcohol consumer	12	7.79
Uninformed	6	3.89

Continuation...

Conclusion		
Variable	N	%
<b>Necessary hospitalization</b>		
Yes	104	67.54
No	50	32.46

Source: Authors (2020)

In were: Patient's medical record

As shown in Table 2, most patients studied (85 - 54.55%) had appropriate BMI at data collection. Furthermore, most patients studied (81 - 52.61%) did not have any comorbidity in the period of data collection, even though the majority (127 - 82.48%) made use of some medication continuously. When investigated the habits of tobacco and alcohol consumption, most of the patients in the study had never smoked (110 - 71.45%) and had never drunk (95 - 61.70%). Of the patients admitted in the emergency care in the period of data collection and who met the study inclusion criteria, the majority (104 - 67.54%) needed hospitalization for treatment of the presented clinical picture.

The history of the current disease, i.e., of the cancer on treatment was analyzed at data collection (Table 3).

Table 3 – History of the cancer on treatment of the surveyed patients – Muriaé – Minas Gerais – Brazil - 2019

Variable	N	%
<b>Tumor category</b>		
Digestive tract tumor	58	37.68
Hematological	25	16.23
Breast tumor	18	11.68
Other	53	34.41
<b>Stageable tumor</b>		
Yes	130	84.42
No	24	15.58
		Continuation...

Conclusion		
Variable	N	%
<b>Tumor staging</b>		
Unstageable tumor	25	16.26
Stage I	13	8.44
Stage II	20	12.98
Stage III	43	27.92
Stage IV	50	32.46
Uninformed	3	1.94
<b>Type of chemotherapy in use</b>		
Outpatient	132	85.71
Inpatient	22	14.28
<b>Chemotherapy purpose</b>		
Palliative	57	37.03
Neoadjuvant	40	25.97
Adjuvant	37	24.02
Curative	20	12.98
<b>Treatment modality</b>		
Exclusive CT	115	74.68
CT and RT	39	25.32
<b>CT administration route</b>		
Intravenous	145	94.18
Oral	5	3.24
Subcutaneous	3	1.94
Intrathecal	1	0.64

Source: Authors (2020)

In were: Patient's medical record

The analysis of Table 3 allows inferring that a large proportion of the studied patients were treating tumors of the digestive tract (58 - 37.68%), stageable (130 - 84.42%), with superiority of tumors at stage III and IV (83 - 53.89%). When checked the treatment at data collection, most patients were on exclusive chemotherapy (115 - 74.68%), with palliative purpose (57 - 37.03%) and intravenous administration (145 - 94.18%). The average number of cycles of chemotherapy performed was 3.88 (+ 4.1 cycles, 1-29 cycles and Mode: 1).

The occurrence of gastrointestinal and hematological toxicities in patients admitted to the emergency room was analyzed in the period of data collection (Table 4).

Table 4 – Frequency of gastrointestinal and hematological toxicities of the surveyed patients – Muriaé – Minas Gerais – Brazil - 2019

<b>Type of toxicity</b>	<b>N</b>	<b>%</b>
Gastrointestinal Toxicity	75	48.70
Hematological Toxicity	65	42.20
Hematological and Gastrointestinal Toxicities	14	9.10
<b>Total</b>	<b>154</b>	<b>100.0</b>

Source: Authors (2020)

In were: Patient's medical record

The analysis of Table 4 allows inferring that, of the 154 patients studied, the majority presented gastrointestinal toxicity (75 - 48.70%). Of the 65 patients who presented hematological toxicity, the majority (40 - 61.53%) presented toxicity grade 4. The main symptoms found in patients were investigated according to each type of toxicity presented (Table 5).

Table 5 – Symptoms according to the type of toxicity of the surveyed patients – Muriaé – Minas Gerais – Brazil – 2019

<b>Type of toxicity</b>	<b>Presented symptom</b>	<b>N</b>	<b>%</b>
<b>Hematological Toxicity Grade 3</b>	Hb <8.0 - 6.5g/dl	16	47.07
	Neutropenia <1,000 - 500 un/l	13	38.23
	Thrombocytopenia 50,000 - 25,000	5	14.70
<b>Total</b>		<b>34</b>	<b>100</b>
<b>Hematological Toxicity Grade 4</b>	Febrile neutropenia	32	44.46
	Neutropenia 500 un/l	26	36.11
	Thrombocytopenia < 25,000	10	13.88
	Hb < 6.5g/dl	4	5.55
<b>Total</b>		<b>72</b>	<b>100</b>

Continuation...

Conclusion			
Type of toxicity	Presented symptom	N	%
<b>Gastrointestinal Toxicity</b>	Vomiting	52	43.72
	Diarrhea	26	21.84
	Nausea	24	20.16
	Mucositis	9	7.56
	Constipation	6	5.04
	Anorexia	2	1.68
<b>Total</b>		<b>119</b>	<b>100</b>

Source: Authors (2020)

In were: Patient's medical record

According to Table 5, the patients with symptoms of hematological toxicity presented with greater frequency Hb <8.0 - 6,5g/dl (16 - 47.07%), which characterizes toxicity grade 3 and in cases of toxicity grade 4, the most identified symptom was the febrile neutropenia (32 - 44.46%). In patients with gastrointestinal toxicity, the most common symptoms were vomiting (52 - 43.72%) followed by diarrhea (26 - 21.84%) and nausea (24 - 20.16%).

The existence of association between the studied independent variables and the type of toxicity presented by the patient was verified. Table 6 shows the variables that presented significant associations.

Table 6 – Variables with significant association in the surveyed patients – Muriaé – Minas Gerais – Brazil – 2019

Variable	Type of toxicity			Total	P statistics*
	Hematological	Gastrointestinal	Hematological and Gastrointestinal		
	n(%)	n(%)	n(%)		
Chemotherapy purpose					
Palliative	24 (15.48%)	30 (19.48%)	3 (1.94%)	57	0.01
Neoadjuvant	14 (9.09%)	21 (13.63%)	5 (3.24%)	40	
Adjuvant	11 (7.14%)	21 (13.63%)	5 (3.24%)	37	
Curative	16 (10.38%)	3 (1.94%)	1 (0.64%)	20	

Continuation...

Concusion					
Variable	Type of toxicity			Total	P statistics*
	Hematological	Gastrointestinal	Hematological and Gastrointestinal		
	n(%)	n(%)	n(%)		
Treatment modality					
Exclusive CT	55 (35.71%)	48 (31.16%)	12 (7.79%)	115	0.01
CT and RT	10 (6.49%)	27 (17.53%)	2 (1.29%)	39	
Type of tumor					
Digestive tract tumor	20 (12.98%)	31 (20.12%)	7 (4.54%)	58	0.02
Hematological	19 (12.33%)	4 (2.59%)	2 (1.29%)	25	
Breast tumor	6 (3.89%)	10 (6.49%)	3 (1.94%)	19	
Tumor staging					
Unstageable tumor	19 (12.33%)	4 (2.59%)	2 (1.29%)	25	0.02
Stage I	5 (3.24%)	5 (3.24%)	3 (1.94%)	13	
Stage II	6 (3.89%)	12 (7.79%)	2 (1.29%)	20	
Stage III	13 (8.44%)	26 (16.88%)	4 (2.59%)	43	
Stage IV	20 (12.98%)	27 (17.53%)	3 (1.94%)	50	
Smoking					
Never smoked	52 (33.76%)	49 (31.81%)	9 (5.84%)	110	0.04
Quit smoking	12 (7.79%)	15 (9.74%)	4 (2.59%)	31	
Active smoker	0	11 (7.14%)	1 (0.64%)	12	

Source: Authors (2020)

In were: \*Chi-Square Test. Source: Patient's medical record

The analysis of Table 6 allows inferring that there is a difference in the proportion of distribution of patients between the different types of toxicity and the treatment. There was a higher proportion of gastrointestinal toxicity in patients undergoing palliative chemotherapy and a greater proportion of hematological toxicity among patients undergoing chemotherapy. There was a higher proportion of gastrointestinal toxicity in patients with tumors of the digestive system and at stage IV. There is a greater proportion of hematological and gastrointestinal toxicity in patients who have never smoked. There were no significant associations between the type of toxicity presented by the patient and the variables age, sex,



comorbidities, medication of continuous use, BMI, alcohol consumption, income and schooling.

## 4 DISCUSSION

The findings of this study indicate that most surveyed patients were from neighboring cities to the institution, considered a reference for the oncologic treatment for the health macro-region. According to the UHS (Unified Health System) pact in the state of Minas Gerais, the institution meets 3 macro-regions and 12 micro-regions, which is equivalent to 158 municipalities and 2,303,371 people, covering other two states and patients from the complementary health. This fact corroborates the national scientific data that map the distribution of incidence of cancer by geographic region, and shows that the southeast region concentrates more than 60% of the incidence of cancer cases, followed by Northeast (27.8%) and South (23.4%), which confirms the importance of the existence of structured and reference macro-regional services in oncologic area in this region (INCA, 2019).

The study showed a higher proportion of occurrence of toxicity in female patients (55, 20%). Factors related to the profile of the patient may also influence the risk of toxicity to chemotherapy (QUEIROGA, 2017). Costa (2012) reports that the individual characteristics of the patient may alter the effects of medication and that, in women, hormonal pharmacokinetic routes and the pattern of use of drugs seem to favor a higher incidence of adverse reactions to drugs. In this study, the greater prevalence of female patients is believed to result from the greater prevalence of breast cancer in the institution. Importantly, the digestive tract tumors, which were the most prevalent in the study, are the third most prevalent in the institution. Historically, women have a habit of seeking medical care earlier than men, which may have contributed to the greater prevalence of female patients in the studied sample.

In this study, 38.31% of patients had incomplete elementary education. This finding corroborates the sociodemographic data monitored by the institution, whose most patients under treatment have incomplete elementary education. The literature indicates a higher concentration of cancer in those with less schooling (SOUZA; SIMÃO; LIMA,2012). In addition to being related to the cancer diagnoses in more advanced stages and to the higher mortality, low educational level is associated with worse standards of health care, which is worrying, since the degree of understanding of peculiarities of the disease and treatment is related to the patients' adherence to the treatment, prevention and management of toxicities (CIRILO; SILVA; FULY; MOREIRA,2016). In this sense, health institutions and professionals need to be ready to meet this profile of patient, adapting their work processes, tools and language to the demands brought by this public, who may have poor knowledge about the disease, treatment and care necessary to minimize the occurrence of problems related to treatments.

The present study also showed that most patients admitted to the Emergency Department of the institution have an income of up to 3 minimum wages (64.30%), justified by the greater prevalence of patients whose professions were "housekeeper" and "rural worker". The socioeconomic status is associated with an increased risk of toxicity induced by chemotherapy. The study showed that patients with low socioeconomic situation presented higher hematological toxicity grades 3 and 4, with chances of occurrence of 84% and 50%, respectively (IUCHNO; CARVALHO, 2019). A lower income is believed to contribute to a delay in the recognition of the symptoms of toxicity and the inability of the patient to seek specialized care. In this sense, health institutions need to have greater surveillance in relation to chemotherapy toxicity and act in providing the proper care for the management of treatment to low-income patients on chemotherapy.

In relation to variables related to health conditions, this study identified that most (54.55%) of the patients had BMI within normal parameters. The maintenance of a BMI within the parameters of normality is important to keep the patient's

nutritional state balanced, contributing to better coping with the chemotherapy treatment. The results reinforce the importance of nutritional assessment and follow-up of these patients in order to guide them concerning adequate food, contributing to the control of the symptoms of toxicities since the first cycle of oncological treatment. Patients under adequate nutritional monitoring have increased survival and adapt better to the chemotherapeutic treatment regimens (QUEIROGA *et al*,2017).

Most of the patients in the study had no comorbidities associated with cancer. Nevertheless, as described by Santos *et al.* (2018), this study showed that 65% of the patients had comorbidities, with hypertension and diabetes as the most prevalent. Barbosa (2018) describes that factors such as the presence of comorbidities interfere in the risk of the patient present hematological toxicity during the chemotherapy treatment. The presence of comorbidities associated with cancer deserves attention by the care team, once cancer is a chronic disease, with a long treatment, in which the patient is exposed to schemes of polychemotherapy and concomitant medications, giving rise to drug interactions (BERTOLAZZI *et al*, 2015). In this sense, the nursing team in contact with the patient needs to act as multipliers of information on prevention and identification of symptoms of toxicity to chemotherapy and assure the maintenance of treatment of pre-existing pathologies. The work of the clinical pharmacist is equally important, supervising and monitoring the treatment, performing pharmacotherapeutic advice during all cycles of treatment and follow-up of toxicities, in a shared and interdisciplinary care network.

When investigating the occurrence of hematological and gastrointestinal toxicity in patients in the present study, most of the participants presented gastrointestinal toxicity (48.70%) and, of those with hematological toxicity, the majority (61.53%) presented toxicity grade 4.

As identified in the literature, the gastrointestinal toxicity to chemotherapeutic agents manifests with symptoms such as nausea and vomiting,

mucositis, anorexia, diarrhea and constipation (RIUL; AGUILAR, 1999). Another study, when verifying the prevalence of gastrointestinal symptoms of patients on chemotherapy, identified that 60% had gastrointestinal toxicity, and the most prevalent symptoms were nausea and vomiting 83.2%, constipation and diarrhea 38% and mucositis 20.2% (SANTOS; SILVA; SANTOS; SOUZA, 2018). As described in the literature, the presence of symptoms such as late nausea and vomiting caused by chemotherapy is especially problematic for patients, with difficult management in clinical practice and can produce more hospitalizations and visits to emergency and outpatient rooms (QUEIROGA, *et al*, 2017).

Other studies in the literature also describe the occurrence of hematological toxicity. A study observed that, in the adjuvant treatment, 26 patients had episodes of febrile neutropenia and 30.4% of them were hospitalized during the chemotherapy treatment, being 33.33% due to febrile neutropenia, causing delays of 6.3 days on average between cycles of chemotherapy (FERREIRA and FRANCO, 2017). Corroborating these data, Avila *et al.* (2013) describe that the antineoplastic agents comprise the main pharmacological group responsible for hospital admissions due to adverse reactions to medications. In this context, health professionals can act to prevent and/or mitigate the occurrence of chemotherapy-induced toxicities, since are more expected events than to other medications (BERTOLAZZI *et al*, 2015). In this sense, the nursing staff plays a key role in basic knowledge on the characteristics, mechanisms of action and effects of drugs in each chemotherapy protocol, in addition to the correct and timely identification of signs and symptoms of toxicity, proposing a plan of individualized care, focusing on reduced individual risks and of suspension or delay in chemotherapy treatment.

The main symptoms found according to the type of toxicity were, in hematological toxicity grade 3, Hb: 8.0 - 6.5 g/dl (47.05%), and in hematological toxicity grade 4, most of the surveyed patients (44.44%) presented febrile neutropenia. A study conducted by Ávila *et al.* (2013) showed that 73.3% of the patients analyzed showed a decreased number of erythrocytes, 66.7% presented

decreased levels of hemoglobin and hematocrit, 73.3% of the patients presented leukopenia, and all patients had at least three elements related to changes in the number of white blood cells count. Almost all chemotherapeutic agents are toxic to the bone marrow, causing myelosuppression or myelotoxicity, which is not only the most common and important adverse event, but also has greater potential for lethality (BONASSA, 2012). Patients undergoing chemotherapy must be carefully monitored regarding the occurrence and duration of myelosuppression, and the nurse is responsible for clarifying the patient regarding the time elapsed between the application of the drug and the lowest value of hematological count, which usually occurs on the 14th day of the cycle of chemotherapy (BONASSA, 2012), alerting the patient regarding risks related to infection, and recognition of signs and symptoms to seek medical care immediately.

In gastrointestinal toxicity, the main symptom found in the research participants was vomiting (43.69%). A study conducted with patients on chemotherapy treatment identified as the most prevalent gastrointestinal symptoms nausea and vomiting (83.2%), constipation and diarrhea (38%) and mucositis (20.2%) (SANTOS *et al*, 2018). Another study identified symptoms such as nausea, diarrhea and vomiting as the main reactions resulting from chemotherapy in relation to gastrointestinal toxicity, which can affect the nutritional condition, hydroelectrolytic balance and quality of life of these patients (GUIMARÃES *et al*, 2015). The same claims that the discomfort provoked by nausea and vomiting in the patient contributes greatly to reducing the quality of life, since patients become weak and without willingness to properly perform their daily chores. Furthermore, the patient begins to eat less than usual, leading them to lack of appetite, anorexia and weakness, which may contribute to worsen his/her overall clinical status, and may even lead to the abandonment of treatment. The presence of symptoms such as late nausea and vomiting caused by chemotherapy is particularly problematic for patients, with difficult management in clinical practice and can produce more hospitalizations and visits to emergency and outpatient rooms (QUEIROGA, *et al*,

2017). In this sense, the nurse needs to evaluate the need for monitoring the patient's nutritional status, acceptance of the diet offered to identify irritating foods that contribute to increased or decreased occurrence of vomiting. Greasy foods, too hot, spicy, salty, with strong odors, fried food and sweets tend to increase the symptoms of nausea and vomiting, and should be contraindicated, whereas solid, acid and cold foods tend to minimize them (BONASSA, 2012).

There was an association between the variables chemotherapy purpose, treatment modality, type of cancer, tumor staging, smoking, and the occurrence of toxicities studied.

Concerning the treatment to which patients were submitted during the period of data collection, most of them (74.67%) were on exclusive palliative chemotherapy (37.01%) and with intravenous administration (94.15%), with an average of 3.88 cycles already made. The so-called "palliative" chemotherapy aims to control symptoms (improving the quality of life), not affecting the survival of patients. A study aiming to evaluate the toxicity and possible changes in the quality of life in patients on chemotherapy identified in 57.7% of patients, the chemotherapy was adjuvant, and in 42.3%, palliative. The same study shows that there was no significant difference in toxicity between cycles or between the adjuvant and palliative treatments (ROQUE; FORONES, 2006). With respect to time of the cycle in which symptoms of toxicity occurred, as pointed out in the literature, 58.6% of the patients who were performing the 5th cycle of chemotherapy showed symptoms of gastrointestinal toxicity (SANTOS *et al*, 2018). According to Souza (2011), despite less aggressive treatments available for the most advanced stages of the disease, the progression of the disease favors the occurrence of symptoms that may contribute to increasing stress and damage to the person's quality of life. The nurse and his/her team is responsible for identifying, preventing and alleviating these symptoms, implementing specific interventions beyond the symptomatic treatments. The professionals must be trained to deal with this

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profile of patient, understanding that cancer is a chronic disease and palliative care is an alternative to provide comfort to the patient.

Therefore, the most advanced stages of the disease bring with them a greater possibility of developing complications related to the treatment, as well as an increased of symptoms related to the disease by directly affecting the patients' quality of life, their health condition and tolerance in relation to the treatment, which may result in suspension or even abandonment of treatment by the patient. In this sense, nursing has a fundamental role in the identification and control of these signs and symptoms, in order to assure immediate intervention and minimize harmful effects already described. The study by Barbosa (2018) describes that 60% of the patients analyzed had a delay between cycles and weeks of treatment, 50%, reduction of doses between cycles and weeks of treatment and 33.3%, suspension of treatment due to the occurrence of toxicity. The study reported 67 delays, with an average of 5.02 days, and the main reasons for delays were symptoms related to hematological and gastrointestinal toxicities. (BARBOSA, 2018). The literature describes that approximately 57.2% of the patients reach health services already presenting advanced lesions that compromise their prognosis, and that, if this situation were different, the occurrence of adverse events caused by chemotherapy treatment could decrease significantly (BARBOSA, 2018). The objective of the chemotherapeutic treatment is to achieve complete control of the tumor, its partial reduction or elimination of residual neoplastic cells (BONASSA, 2012). In this sense, the cancellation or postponement of chemotherapy may have implications related to the patient's health condition, reflecting on the symptoms related to the disease, impacting on the costs related to the care, decreased survival of patients and increased mortality.

Regarding the type of cancer under treatment, a large proportion of the surveyed patients were on treatment of digestive tract tumors (37.66%), stageable (84.41%), with a superiority of tumors at stage III and IV (53.89%). Corroborating the results found, a study that sought to monitor and assess the occurrence and

the degree of intensity of nausea, vomiting and diarrhea in patients undergoing chemotherapy identified that, in relation to the staging, 47.0% of the patients were at stage III, 35.3% at stage IV (ALMEIDA; GUTIÉRREZ; ADAMI, 2004). In relation to the advanced stage of cancer and the presence of chemotherapy toxicity, Souza (2011) describes that the state of personal performance based on the patient's performance status is the best indicator of risk assessment versus the benefit to the patient on oncological treatment. In this way, if the condition of performance is restricted, there is a higher probability of the person develop serious adverse effects of chemotherapy toxicity. A study conducted by Roque and Forones (2011) showed no statistical significance regarding the toxicities when comparing the individuals on adjuvant or palliative treatment. It is well known that, despite being a right acquired in Law 12,732, of 2012, which stipulates the onset of cancer treatment by the UHS in a maximum of 60 days since the diagnosis, there is a commitment in relation to the balanced and full access of the population to the diagnosis and treatment of cancer, which ultimately jeopardize the survival and quality of life of these patients. Thus, the municipal and state health departments are responsible for the appropriate agreement in health regions regarding access to health services, in addition to establishing methodologies that ensure early diagnosis and the establishment of timely reference and counter-reference flows of care with patients with cancer by specialized centers.

Importante relatar que a literatura descreve também a ausência de consumo prévio de álcool e de tabaco como fator de risco para toxicidade gastrointestinal (MOURA,2017). Não se trata aqui de ir na contramão das inúmeras evidências científicas de que fumar e beber são danosos aos pacientes em tratamento do câncer, porém torna-se necessário apresentar as descrições da literatura onde o uso prévio do etilismo e do tabaco são descritos como fatores que minimizam os efeitos relacionados a toxicidade gastrointestinal a quimioterapia. Há que se ressaltar que apesar a maioria das evidencias apontam os hábitos de tabagismo e etilismo como importantes fatores de risco para o surgimento e progressão do



câncer conforme apontamento do estudo realizado por Jemal (2019) que descreve o uso do tabaco e álcool como fatores de risco para o desenvolvimento e agravamento de vários tipos de câncer.

In this study, most patients (71.42%) had never smoked nor drunk, and there was a greater proportion of hematological and gastrointestinal toxicity in patients who had never smoked, corroborating the results found in the literature. This study describes that 55.1% of patients on chemotherapy reported alcohol consumption, and 51.7% smoking. Tobacco and alcohol lead the patient to tolerate symptoms of gastrointestinal toxicity to chemotherapy (QUEIROGA *et al*, 2017). Importantly, the literature also describes the absence of prior consumption of alcohol and tobacco as a risk factor for gastrointestinal toxicity (MOURA, 2017). The aim here is not to contradict the scientific evidence from several researches that smoking and drinking are harmful to patients on cancer treatment, but it is necessary to present the descriptions in the literature in which previous use of alcohol and tobacco are described as factors that minimize the effects related to the gastrointestinal toxicity to chemotherapy. The evidence mostly suggests smoking and drinking habits as important risk factors for the onset and progression of cancer as highlighted by the study conducted by Jemal (2019), which describes the use of tobacco and alcohol as risk factors for the development and worsening of several types of cancer.

## 5 CONCLUSIONS

In this study, 48.70% of patients had gastrointestinal toxicity followed by 42.20% of hematological toxicity and 9.10% with hematological and gastrointestinal toxicities. In patients with gastrointestinal toxicity, the main symptoms were vomiting (43.72%), diarrhea (21.84%), nausea (20.16%), mucositis (7.56%), constipation (5.04%) and anorexia (1.68%). In patients with hematological toxicity grade 3, the main symptoms presented were the Hb <8.0 - 6,5g/dl (47.07%),

neutropenia <1,000 - 500 un/l (38.23%) and thrombocytopenia 50,000 - 25,000 (14.70%). In patients with hematological toxicity grade 4, the main symptoms were febrile neutropenia (44.46%), neutropenia 500 un/l (36.11%), thrombocytopenia < 25,000 (13.88%) and Hb < 6.5g/dl (5.55%).

The variables that presented association with the study outcomes were the chemotherapy purpose, treatment modality, type of cancer, staging and smoking. There was a higher proportion of gastrointestinal toxicity in patients undergoing palliative chemotherapy, with digestive tract tumors and at stage IV and a greater proportion of hematological toxicity among patients undergoing exclusive chemotherapy. There was a greater proportion of hematological and gastrointestinal toxicity in patients who had never smoked.

The data analysis will allow fostering the planning, by the institution, of the description and application of more specific protocols to prevent toxicities, individualizing the care, allowing the prevention or minimization of the effects of treatment, in order to avoid hospitalizations or interruptions of chemotherapy sessions due to the patient's clinical worsening.

From this perspective, the nurse must have competences to evaluate the individual on chemotherapy treatment through nursing consultations before and after chemotherapy, identifying potential problems that can suffer interventions to prevent and/or minimize toxicities, such as life and nutritional habits, personal hygiene, self-care, awareness of their illness and therapeutic management, housing conditions, family dynamics and support, among other issues, which considerably affect the emergence of complications from chemotherapy treatment and that can lead to hospitalization and treatment interruption.

Furthermore, the professionals working in the health care network should be trained to identify and handle the signs and symptoms presented by oncologic patients from chemotherapy, for adequate establishment of reference and counter-reference flows, conforming a healthcare network based on health promotion, disease prevention, health education and encouragement to self-care.

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