

PREVALENCE OF POLYPHARMACY IN ELDERLY PATIENTS UNDERGOING CAPECITABINE AND OXALIPLATIN THERAPY

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Abstract

Advanced age is a risk factor for Gastric and colorectal cancer development. Chemotherapy combining oral capecitabine and intravenous oxaliplatin (XELOX) is a therapeutic strategy for these cancer types. Polypharmacy is defined as the use of four or more medications by a patient and is more prevalent among older adults with cancer compared to older adults without cancer. The objective of this study is to identify polypharmacy and the use of potentially inappropriate medications (PIMs) in older patients undergoing XELOX. This is a retrospective and prospective longitudinal analytical. Data were collected from the pharmacotherapeutic follow-up forms of patients aged 60 years or older, with a confirmed diagnosis of gastric or colorectal cancer. A total of 22 patients met the inclusion criteria. All study participants presented polypharmacy. After oncologic and supportive drugs, the most frequently used medications were antihypertensives (81.8%), psychotropics (40.9%), and antidiabetics (31.8%). The study showed that 82% of patients used at least one PIM. A total of 89 potential drug interactions were identified. Total number of medications used by patients was positively associated with PIM use and the number of drug interactions. Pharmacists can help minimize harmful polypharmacy and the impact of multiple medication use in older cancer patients.

Key Words: colorectal neoplasms, stomach neoplasms, polypharmacy, health of the elderly, drug interactions.

Resumo

O câncer gástrico e colorretal estão entre os cinco mais frequentes no Brasil. Idade avançada é fator de risco para o desenvolvimento da doença. A quimioterapia que combina capecitabina oral e oxaliplatina intravenosa (XELOX) é uma das estratégias terapêuticas para esses tipos de câncer. Polifarmácia é o uso de quatro ou mais medicamentos por um paciente e é mais prevalente entre idosos com câncer em comparação com idosos sem câncer. O objetivo do estudo é identificar a polifarmácia e o uso de medicamentos potencialmente inapropriados (MPI) em pacientes idosos submetidos ao protocolo. Trata-se de um estudo analítico longitudinal retrospectivo e prospectivo. Os dados foram coletados a partir dos formulários de acompanhamento farmacoterapêutico de pacientes com 60 anos ou mais, com diagnóstico de câncer gástrico ou colorretal. 22 pacientes preencheram os critérios de inclusão. Todos os participantes do estudo (100%) apresentaram polifarmácia. Após os medicamentos oncológicos e de suporte, os fármacos mais frequentemente utilizados foram

antihipertensivos (81,8%), psicotrópicos (40,9%) e antidiabéticos (31,8%). O estudo mostrou que 82% dos pacientes utilizaram pelo menos um MPI. Foram identificados 89 potenciais interações medicamentosas. O número total de medicamentos utilizados pelos pacientes esteve positivamente associado ao uso de MPI e ao número de interações medicamentosas.

Palavras chave: neoplasias colorretais, neoplasias gástricas, polimedicação, saúde do idoso, interações medicamentosas.

1 Introdução

The aging of Brazilian population over the past 100 years has led to a change in the epidemiological profile, characterized by an increased prevalence of non-communicable chronic diseases (Alves *et al.*, 2020; Brasil, 2025). In this context, the elderly population is more susceptible to malignant neoplasms, primarily due to prolonged exposure to carcinogenic agents and age-related impairments in cellular repair mechanisms (Alves *et al.*, 2020; Turner; Shakib; Bell, 2017).

Polypharmacy is defined as the regular use of four or more medications simultaneously by a single patient, encompassing prescription drugs, over-the-counter (OTC) medications, and traditional therapies. This phenomenon has emerged as a public health concern due to its association with adverse drug reactions, drug interactions, and increased healthcare costs. The condition is particularly prevalent among elderly cancer patients when compared both to non-cancer elderly individuals and to younger patients undergoing oncological treatment (Alves *et al.*, 2020; ISMP Brasil, 2018; Khaledi; Kazemi; Tahmasebi, 2019).

The high prevalence of polypharmacy is also associated with increased use of potentially inappropriate medications (PIMs) for older adults. PIMs are defined as medications for which the potential risks may outweigh the benefits in older individuals and are significantly associated with adverse drug reactions, high potential for interaction with other pharmacological agents drug, hospitalizations, low treatment adherence and mortality among geriatric cancer patients. (Sharma *et al.*, 2016).

Gastric and colorectal cancers are among the five most common types of cancer both in Brazil and worldwide, particularly among the elderly population, with age being one of the main risk factors for disease development (Instituto Nacional do Câncer (Brasil), 2022). Among the treatment options is chemotherapy with the XELOX regimen, which combines oral capecitabine and intravenous oxaliplatin. Additionally, supportive medications are frequently administered to minimize chemotherapy-related adverse effects such as nausea, vomiting, and diarrhea (Instituto Nacional do Câncer, [S.d.]; Katz, 2017).

Identifying polypharmacy and the use of potentially inappropriate medications (PIMs) is crucial to reducing the risk of adverse events, non-adherence, and hospitalizations, while also optimizing treatment efficacy. The objective of this study is to identify the occurrence of polypharmacy and the use of PIMs in elderly patients

undergoing chemotherapy with the XELOX regimen for the treatment of gastric and colorectal cancers.

2 Method

This is a longitudinal analytical study with both retrospective and prospective components, conducted from July 2020 to October 2021. The study included all patients aged 60 years or older, of both sexes, with a confirmed diagnosis of gastric or colorectal cancer through clinical and laboratory examinations, who underwent chemotherapy with capecitabine and oxaliplatin at a federal hospital of the Brazilian Unified Health System (Sistema Único de Saúde – SUS). Patients with neurological disorders resulting in cognitive impairment that could hinder comprehension at any stage of the study were excluded.

Data was collected during the pharmacotherapeutic follow-up of patients using a semi-structured form.

Potential drug interactions were assessed using the Medscape® database. Patients were considered to be experiencing polypharmacy when they were routinely and simultaneously using four or more medications. Potentially inappropriate medications (PIMs) for older adults were identified according to the 2023 American Geriatrics Society Beers Criteria®¹⁰.

Data was registered in spreadsheets and presented in graphs and/or tables using Microsoft Excel®. Descriptive statistical analysis was conducted for sociodemographic variables, including gender and age, as well as for clinical variables such as drug-related problems (DRPs), the use of PIMs, drug interactions, adverse drug reactions, and the number of pharmaceutical interventions performed. Hypothesis tests were performed to assess correlations between these variables and the variable “polypharmacy.”. The independent t-test was applied to analyze the relationship between two variables (one categorical and one numerical) in two independent groups, assuming normal distribution and homogeneous variance. For variables that did not meet the assumptions of normality and homogeneity, the Mann–Whitney U test was used. The Pearson correlation coefficient was used for variables with a normal distribution, and the Kendall correlation coefficient was used for variables that were not normally distributed. The Shapiro–Wilk test was applied to assess normality and detect outliers, while Levene’s test was used to assess the homogeneity of variances. All statistical analyses were conducted using RealStatistics, an add-on software that extends the built-in statistical functions of Microsoft Excel®.

The study was approved by the Research Ethics Committee (CAAE: 39906820.6.0000.5243) in compliance with the Directives 466/2012 (Brasil, 2013) and 510/2016 (Brasil, 2016) of the National Health Council. All participants who agreed to take part in the study signed an informed consent form.

3 Results

A total of 22 patients participated in the study, comprising 14 men and 8 women. Among them, 86.4% were diagnosed with colorectal cancer. Participant ages ranged from 60 to 78 years, with a mean age of 66.9 years. The age group with the highest number of gastric cancer cases was 71–78 years, accounting for 66.7% of those patients. For colorectal cancer, the number of patients was evenly distributed between the age groups of 60–65 and 66–70 years, each representing 42.1% of cases.

Following oxaliplatin, capecitabine, and supportive medications such as ondansetron and dexamethasone, which were used by 100% of the patients, the most frequently prescribed drugs were antihypertensives (81.8%), particularly losartan (59.1%) and atenolol (27.3%). Psychoactive medications were used by 40.9% of patients, with tramadol (13.6%) and clonazepam (9%) being the most common. Oral hypoglycemic agents were used by 31.8% of patients, mainly metformin (18.2%) and gliclazide (13.6%). Omeprazole was reported in 13.6% of the cases. Figure 1 presents the distribution of these medications

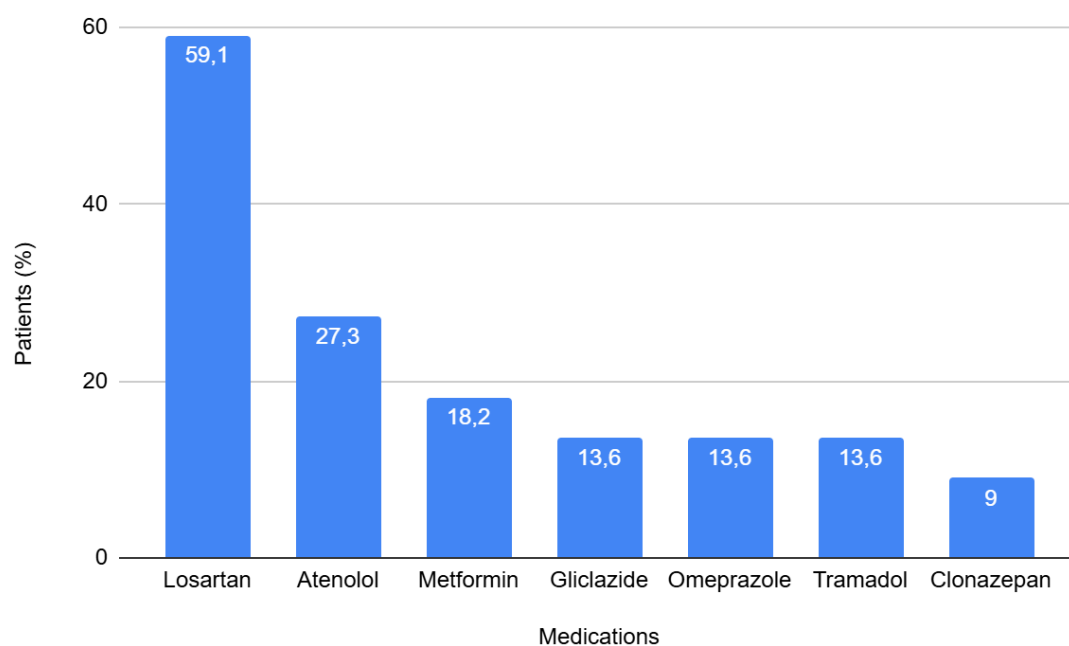


Figure 1. Distribution of the most frequently used medications among patients undergoing XELOX treatment, 2022.

Fonte: as autoras, 2025

Based on the 2023 Beers Criteria, the use of 16 different potentially inappropriate medications (PIMs) was identified. The analysis showed that 82% of the patients included in the study used at least one PIM. Among these patients, 7 individuals—corresponding to a portion of that 82%—used two or more PIMs.

Benzodiazepines were used by 18% of the patients and, as recommended by the Beers Criteria, should be avoided in older adults due to their increased sensitivity to these

drugs and reduced capacity to metabolize long-acting agents of this class, such as clonazepam and diazepam. Moreover, the concomitant use of opioids—a common combination in oncology patients—may result in profound sedation and respiratory depression (American Geriatrics Society Beers Criteria® Update Expert Panel., 2023)

Omeprazole and tramadol were also frequently used by patients in the study, each with a prevalence of 14%. Omeprazole use in older adults is associated with an increased risk of *Clostridium difficile* infection, bone loss, and fractures. According to the Beers Criteria, the use of proton pump inhibitors (PPIs) should not exceed 8 weeks, except in patients at high risk (American Geriatrics Society Beers Criteria® Update Expert Panel., 2023).

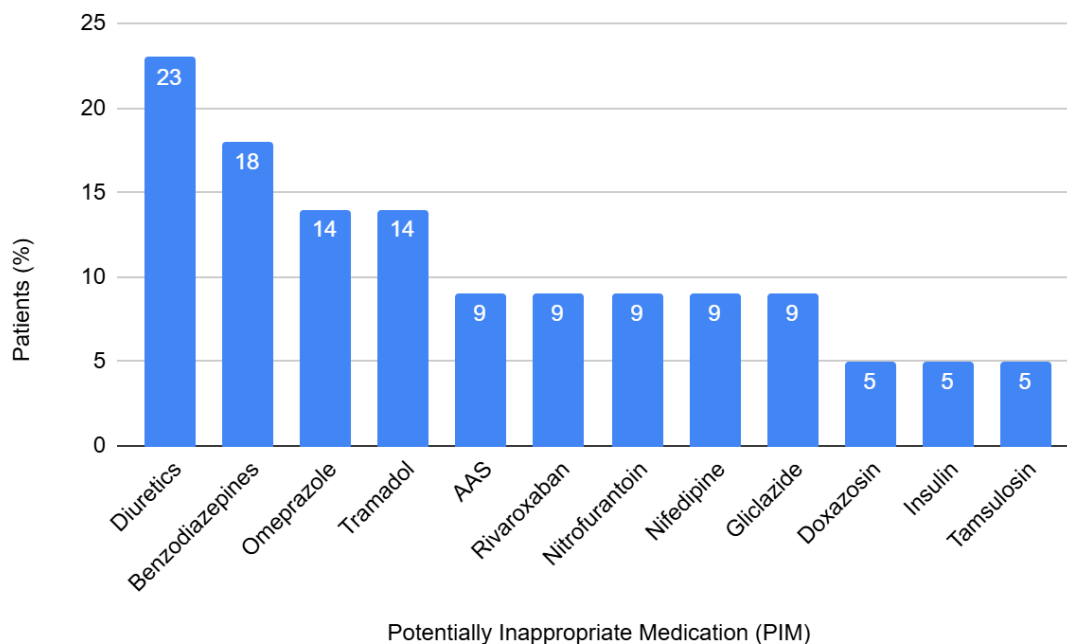


Figure 2. Distribution of elderly patients receiving XELOX chemotherapy, stratified by the most frequently used potentially inappropriate medications, 2022

Fonte: as autoras, 2025

A drug interaction occurs when two medications are administered concurrently and their effects are altered by the presence of one another, potentially modifying the intended therapeutic outcome (Silva, 2022). A total of 89 potential drug interactions were identified among the 202 medications analyzed. Since all 22 patients received antineoplastic agents along with supportive therapy, every patient presented with at least one potential drug interaction, either among the antineoplastic agents themselves or between antineoplastic and supportive care medications.

Given that 100% of the patients in the study were considered polymedicated, all statistical tests included an analysis of the correlation between the number of medications used and both sociodemographic variables ("gender" and "age") and clinical variables (number of potential drug interactions identified, number of drug-related problems, use

of potentially inappropriate medications for older adults, identified adverse drug reactions, and number of pharmaceutical interventions performed).

The correlation between the number of medications used and patient gender was analyzed using the independent samples *t*-test. The *t*-test revealed no significant effect of gender on the number of medications used by the patients ($t(20) = 0.67$; $p = 0.5$). The number of medications used by male patients ($\bar{x} = 5$; $S^2 = 9.60$) did not differ significantly from that of female patients ($\bar{x} = 4$; $S^2 = 2.54$).

The Mann–Whitney U test (a non-parametric test) was conducted to assess the relationship between the use of potentially inappropriate medications (PIMs) and the total number of medications used. The test revealed a significant difference ($U = 3$; $p < 0.005$) in the total number of medications used by patients who were taking PIMs ($Md = 5$; $IQR = 2.5$) compared to those who were not ($Md = 2$; $IQR = 0.5$). Therefore, it can be concluded that a higher number of medications is associated with an increased likelihood of potentially inappropriate medication use in older adults.

To determine the relationship between numerical/quantitative variables, Pearson correlation coefficients were calculated for variables with normal distribution, and Kendall's tau coefficients were used for variables not normally distributed. Table 1 presents the relationships and their respective correlation coefficients.

Table 1. Correlation coefficients for relationships between the number of medications and selected sociodemographic and clinical variables

Variables Tested	Pearson Correlation Coefficient	Kendall's Tau Correlation Coefficient
Number of medications × Age	−0.0072	—
Number of medications × Pharmaceutical Interventions	0.5	—
Number of medications × Drug-Related Problems (DRPs)	—	0.26
Number of medications × Adverse Drug Reactions (ADRs)	—	0.19
Number of medications × Drug Interactions	—	0.42
Number of medications × Potentially Inappropriate Medications (PIMs)	—	0.67

Fonte: as autoras, 2025

Pearson's and Kendall's correlation coefficients are statistical analyses used to measure the strength and direction of the association between two variables. In terms of strength, the correlation coefficient ranges from +1 to -1. A value of ± 1 indicates a perfect association between the two variables. As the coefficient approaches 0, the strength of the relationship weakens. The sign of the coefficient indicates the direction of the relationship: a positive sign (+) denotes a positive relationship, while a negative sign (-) denotes a negative relationship.

4 Discussion

Older adults, in addition to often undergoing cancer treatment, may present with comorbidities such as cardiovascular events and other symptoms related to the disease or its treatment, such as gastrointestinal problems and pain (Shrestha; Shrestha; Khanal, 2019).

The findings, regarding the most commonly used medications, are consistent with those reported by Alano and colleagues (Graziela Modolon Alano; Taís dos Santos Corrêa; Dayani Galato, 2012) who observed a prevalence of medications used to treat cardiovascular system diseases (48.1%) among patients aged 60 years and older, followed by medications acting on the nervous system (16.9%) and on the alimentary tract and metabolism (14.7%).

Like this study, Leger *et al.* (2018) and Mohamed *et al.* (2018) reported polypharmacy prevalence rates of 75.4% and 88%, respectively, among cancer patients. The study by Morio *et al.* (2019) also reported a high prevalence of polypharmacy in cancer patients over 65 years of age, with 84.5% of patients using at least five medications. A cross-sectional study conducted by Kotlinska-Lemieszek *et al.* (2014) among patients with polypharmacy found that patients with advanced cancer used an average of 7.8 medications.

Nam and colleagues (2016), in a study involving hospitalized older adults, found that 81% of patients used at least one potentially inappropriate medication (PIM), a finding consistent with the present study. In contrast, other studies, such as those by Hong *et al.* (2020) and Morio *et al.* (2019), reported lower PIM prevalence rates, ranging from 20% to 48%. This discrepancy in the literature may be attributed to differences in assessment tools and study populations.

Drug interactions must be carefully evaluated in older patients, as they often exhibit significant age-related physiological changes. Therefore, drug interactions appear to be an almost inevitable scenario in elderly oncology patients (Shrestha; Shrestha; Khanal, 2019).

According to guidance from Medscape, the concomitant use of oxaliplatin and ondansetron should be made with caution due to the potential for enhanced pharmacological effects when administered together. Additionally, dexamethasone may interfere with hepatic and intestinal enzyme metabolism, potentially increasing the serum concentration and effects of ondansetron.

Table 2. Most frequent potential drug interactions in patients undergoing XELOX treatment and the corresponding clinical management recommendations, according to Medscape, 2022.

Interacting Drugs	Interaction (Medscape)	Suggested Clinical Management (Medscape)
Oxaliplatin × Ondansetron	May enhance each other's effect and prolong the QT interval	Use with caution and monitor ECG
Ondansetron × Dexamethasone	May increase serum levels of ondansetron due to CYP3A4 metabolism alteration	Use with caution and monitor for adverse reactions
Losartan × Atenolol	Possible increase in serum potassium levels due to pharmacodynamic synergy	Monitor serum potassium levels
Dexamethasone × Rivaroxaban	Reduced effect of rivaroxaban due to CYP3A4 induction	Use with caution and monitor; dose adjustment of rivaroxaban may be needed
Dexamethasone × Tramadol	Decreased levels or effect of tramadol due to hepatic/intestinal CYP3A4 metabolism alteration; reduced AUC of tramadol and active metabolite (O-desmethyltramadol) due to induction of CYP3A4 and CYP2B6	Use with caution and monitor
Dexamethasone × Aspirin (ASA)	May increase each other's toxicity through pharmacodynamic synergy; increased risk of gastrointestinal ulceration	Use with caution and monitor
Dexamethasone × Nifedipine	Increased dexamethasone levels and decreased nifedipine levels due to CYP3A4 alteration; possible reduction in dexamethasone levels due to MDR1 efflux	Use with caution and monitor; consider therapy modification
Nifedipine × Loperamide	Decreased levels and effect of loperamide due to MDR efflux	Use with caution and monitor

Fonte: Medscape, 2022

The literature indicates that approximately 12.63% of older patients are exposed to potentially inappropriate medications (PIMs) based on the Beers Criteria. A study conducted in an oncology outpatient clinic in the United States involving elderly cancer patients reported a 40% prevalence of PIM use (Sharma *et al.*, 2016). Alkan *et al.* (2017) found that among 445 elderly cancer patients, nearly one-third were exposed to potentially inappropriate medications and severe drug interactions. Carvalho *et al.* (2012), in a study conducted in the state of São Paulo with over 2,000 older adults, reported that one in every three individuals used four or more medications, and 15.6% used at least one medication classified as inappropriate. The study also showed that both the number of medical consultations and hospital admissions increased the risk of polypharmacy by 1.9 and 3.8 times, respectively.

The correlation coefficient of -0.0072 found in this study indicates no relationship between patient age and the total number of medications used. However, previous studies have confirmed that advanced age is generally associated with the use of a greater number of medications. This discrepancy may have been negatively influenced by the small sample size of the present study.

Strong correlations were observed between the total number of medications used and the number of potentially inappropriate medications (PIMs) ($r = 0.67$), as well as pharmaceutical interventions ($r = 0.50$). A moderate correlation was found between the number of medications and drug interactions ($r = 0.42$). Weaker correlations were observed between the number of medications and drug-related problems (DRPs) ($r = 0.26$), and adverse drug reactions (ADRs) ($r = 0.19$). These results indicate that patients using a greater number of medications were more likely to have PIMs included in their pharmacotherapy, and that the number of pharmaceutical interventions increased in accordance with the number of medications used.

Similar to the findings of the present study, Hong *et al.* (2020) also reported a relationship between polypharmacy, PIM use, and drug interactions in elderly Korean cancer patients. Morio *et al.* (2019) likewise found that as the number of medications increased, so did the likelihood of drug interactions and the use of potentially inappropriate medications.

One of the limitations of this study was the small number of elderly cancer patients undergoing XELOX treatment during the study period. The lack of a formal validation process for the questionnaire used (pharmaceutical care service form), as well as the absence of psychometric analyses, may have impacted the accuracy and robustness of the findings. Implementing such procedures would contribute to more reliable and consistent data.

5 Conclusion

Polypharmacy and the use of potentially inappropriate medications (PIMs) in older adults were substantially prevalent. A statistically significant association was found between polypharmacy and the risk of PIM use and drug interactions.

Considering that the use of antineoplastic agents and supportive medications is essential for cancer treatment, understanding the risk factors and consequences associated with polypharmacy may help healthcare professionals and care teams manage therapy more effectively. Furthermore, it can support the implementation of measures to reduce polypharmacy, the use of PIMs, and the occurrence of drug interactions. Among the necessary strategies to mitigate harmful polypharmacy and/or manage its consequences is the active role of the pharmacist, whose interventions contribute to minimizing the impact of multiple medication use in older cancer patients.

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