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Identification and evaluation of potential undesirable drug interactions involving oral antineoplastics in patients at a university hospital

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Abstract

Objective: to characterize the clinical profile of patients and the pharmacological profile of undesirable drug interactions in cancer patients with outpatient follow-up. **Methods:** cross-sectional, descriptive and quantitative study carried out in the oncology outpatient clinic of a university hospital. Data were collected from the medical records of 232 patients records on sex, age, pharmacotherapy, diagnosis of neoplasia and other comorbidities. Drug interactions, as well as clinical severity, pharmacological mechanisms, and possible clinical effects were identified and evaluated by the Drug Interactions Checker Software. **Results:** Thirty-one types of undesirable interactions were identified in 23.3% of the medical records of patients whose mean age was 65.5 years, with 59.0% of patients classified as polypharmacy. It was found that 16.0% were of major severity, 81.0% moderate and 3.0% minor. The most common involved: bicalutamide and simvastatin (20.6%), capecitabine and hydrochlorothiazide (14.2%), duloxetine and tamoxifen (7.9%). The pharmacokinetic mechanism was responsible for 35.4% and the pharmacodynamic mechanism, for 45.2% of the interactions. The main clinical effects observed were: prolongation of the cardiac QT interval (41.9%) and reduction of the efficacy of the antineoplastic agent (32.2%). The main comorbidities include: hypertension (63.8%), diabetes (29.7%) and dyslipidemia (18.5%). **Conclusion:** the identified drug interactions are clinically relevant with regard to their potential effects. However, there is a low frequency of interactions, partly due to the limited sample of medical records with data on medications in use duly recorded.

Keywords: drug interactions; antineoplastic agents; polypharmacy; medical oncology

Identificação e avaliação de potenciais interações medicamentosas indesejáveis envolvendo antineoplásicos orais em pacientes de um hospital universitário

Resumo

Objetivo: caracterizar o perfil clínico dos pacientes e o perfil farmacológico das interações medicamentosas indesejáveis em pacientes oncológicos com seguimento ambulatorial. **Métodos:** estudo transversal, descritivo e quantitativo realizado em ambulatório de oncologia de um hospital universitário. Coletou-se dados de prontuários de 232 pacientes sobre sexo, idade, farmacoterapia, diagnóstico de neoplasia e outras comorbidades. As interações medicamentosas assim como a gravidade clínica, os mecanismos farmacológicos e os possíveis efeitos clínicos foram identificados e avaliadas pelo Software Drug Interactions Checker. **Resultados:** Identificou-se 31 tipos de interações indesejáveis em 23,3% dos prontuários de pacientes, cuja média de idade era 65,5 anos, sendo 59,0% pacientes classificados como polifarmácia. Verificou-se que 16,0% eram de gravidade maior, 81,0% moderada e 3,0% menor. As mais comuns envolveram: bicalutamida e sinvastatina (20,6%), capecitabina e hidroclorotiazida (14,2%), duloxetina e tamoxifeno (7,9%). O mecanismo farmacocinético foi responsável por 35,4% e o farmacodinâmico, por 45,2% das interações. Os principais efeitos clínicos verificados foram: prolongamento do intervalo QT cardíaco (41,9%) e a redução da eficácia do antineoplásico (32,2%). As principais comorbidades incluem: hipertensão (63,8%), diabetes (29,7%) e dislipidemia (18,5%). **Conclusão:** as interações medicamentosas identificadas são clinicamente relevantes no que concerne aos seus potenciais efeitos. Todavia, verifica-se baixa frequência de interações, em parte, devido à amostra limitada de prontuários com dados de medicamentos em uso devidamente registrados.

Palavras-chave: interações medicamentosas; agentes antineoplásicos; polimedicação; oncologia.

Introduction

Potential adverse events resulting from drug interactions represent a major public health issue. According to the World Health Organization (WHO), drug interactions are among the leading causes of preventable morbidity and mortality worldwide[1]. In this context, oncology patients are particularly vulnerable to such clinical events due to the pharmacological characteristics of the antineoplastic agents they use—especially when combined with clinical and sociodemographic factors such as age, comorbidities, and polypharmacy[2]. Therefore, the lack of knowledge about the profile of potential drug interactions in patients undergoing oral antineoplastic therapy in outpatient settings poses a significant challenge for prescribers who care for this population, such as clinical oncologists.

By definition, a drug interaction is the alteration of a drug's effect as a result of its interaction with one or more other drugs, which may lead to either a reduction or an increase in therapeutic efficacy[3]. According to the WHO, when a drug interaction leads to an adverse outcome for the patient, it is classified as an adverse drug event (ADE), the likelihood of which depends mainly on the clinical significance of the interaction[4]. The drugs involved may be prescribed medications or over-the-counter products used for self-medication.

Regarding the mechanisms involved, drug interactions are classified as pharmacokinetic, pharmacodynamic, or pharmaceutical in nature. Pharmacokinetic interactions are the most frequent[2]. These interactions interfere with the processes of absorption, distribution, metabolism, and excretion of one or more of the drugs involved[5]. Examples include inhibition or induction of cytochrome P450 (CYP) isoenzymes, induction or inhibition of P-glycoprotein (P-gp) at the enterocyte level, drug chelation within the gastrointestinal tract, competition for plasma protein binding, and reduced or increased hepatic and/or renal clearance of drugs. On the other hand, pharmacodynamic interactions result from the administration of drugs with similar pharmacological effects—leading to additive or synergistic effects—or from the concomitant use of drugs with opposing effects, which may result in a reduction in the efficacy of one or both[6]. Finally, pharmaceutical interactions (incompatibilities) are direct chemical interactions—i.e., physicochemical interactions—that occur when two drugs are administered in the same solution or container, thereby compromising therapeutic safety and efficacy[7].

While oral antineoplastic agents offer greater convenience to patients through the possibility of home administration, they are also more commonly associated with drug interactions compared to parenteral chemotherapy agents. This occurs because oral antineoplastics are more susceptible to presystemic metabolism (e.g., hepatic metabolism) and/or may be substrates of efflux transporters at the enterocyte level, which can affect bioavailability and, consequently, therapeutic efficacy—or even increase the risk of toxicity.

As oral antineoplastic agents become more widely used, the risks of drug interactions rise, particularly because other medications are co-administered in the outpatient setting without supervision from the attending physician or clinical pharmacist.

Furthermore, it is important to emphasize that the number of people diagnosed with cancer is estimated to increase by 50% by 2025 due to population aging and the growing influence of lifestyle-related environmental factors[8]. Consequently, older adults represent a significant proportion of oncology patients, who also present with higher prevalence of comorbidities and polypharmacy. By definition, polypharmacy refers to the daily use of four or more medications—prescribed, over-the-counter, and/or traditional—by a single patient[1]. Undoubtedly, polypharmacy can be considered a problem across all age groups, but it is particularly critical among older adults and stands out as one of the main risk factors for drug interactions. Other contributing factors include the lack of use of tools to identify causality mechanisms and lists of known potential interactions. Therefore, the geriatric population is more vulnerable to adverse drug events, which can influence cancer prognosis and treatment tolerance.

It is concerning that studies dedicated to outlining the profile of drug interactions involving antineoplastic agents are scarce. Moreover, the few available studies are often unable to encompass the diverse therapeutic contexts practiced across different hospital settings. Consequently, the lack of knowledge regarding the interaction profile of drugs used by oncology patients may lead to an increased risk of therapeutic failure and/or adverse events, which could otherwise be prevented through rational prescribing, pharmacotherapy review, and professional guidance provided to patients regarding over-the-counter medications to avoid. In this sense, understanding the profile of these interactions can optimize the safety and efficacy of oncologic treatment while reducing the risk of interactions that may lead to undesirable clinical outcomes.

Given the above, the relevance of this research lies in the need to investigate potential undesirable interactions based on the medications documented in the medical records of patients followed in outpatient oncology care. The lack of quantitative and qualitative information regarding the patients' clinical profile and drug interaction patterns increases the risk of adverse events. Conversely, knowledge of these aspects enables the attending physician to consider possible strategies for preventing adverse events resulting from drug interactions. From this perspective, the aim of this study was to characterize the clinical and sociodemographic profiles of patients, as well as the pharmacological profile of undesirable interactions involving oral antineoplastic agents, and to describe the severity and mechanisms of the identified interactions, based on a sample of patients followed at the oncology outpatient clinic of a university hospital.

Methods

A cross-sectional, quantitative, and descriptive study was conducted at the oncology outpatient clinic of the Hospital das Clínicas of the Federal University of Pernambuco (HC-UFPE), which is part of the Brazilian Company of Hospital Services (EBSERH). The investigation was approved by the Research Ethics Committee (CEP) of HC-UFPE, under the Certificate of Presentation for Ethical Consideration (CAAE) number 75954923.8.0000.8807, with approval granted on November 28, 2023.

Eligible medical records included those of patients followed at the clinical oncology outpatient clinic of HC-UFPE (EBSERH network) between January 2023 and April 2024. Exclusion criteria included medical records of patients without any medication records, those using only one drug, those receiving exclusively intravenous antineoplastic therapy, and those who did not use oral antineoplastic agents during the study period.

Data were collected through consultation of the Hospital Management Application for University Hospitals (AGHUx), and included information on antineoplastic therapy (chemotherapy and hormonal therapy), other medications in use (non-antineoplastic), comorbidities, age, sex, and type of neoplasm according to primary site. However, information related to the clinical staging of the disease was not collected due to the lack of standardized documentation in the electronic medical records. This limitation is relevant, as patients with metastatic disease tend to have a higher number of comorbidities, more intensive medication use, and an increased risk of adverse events.

The dependent variable in this study consisted of the presence of undesirable potential drug interactions between oral antineoplastic agents and other concomitantly used medications. These interactions were identified using the Drug Interactions Checker (Drugs.com®) software, whose database integrates information from sources such as Micromedex, Cerner Multum, the American Society of Health-System Pharmacists (ASHP), among others. Based on the information available in the consulted database, interactions were classified according to severity (minor, moderate, or major) and mechanism of action (pharmacokinetic, pharmacodynamic, or mixed).

The independent variables included the patients' sociodemographic characteristics (sex and age), recorded comorbidities, type of neoplasm, and pharmacotherapy (antineoplastic and non-antineoplastic drugs), as well as the total number of medications in use.

Data collection was carried out by a pair of researchers through double data entry from the specified institutional database, with the aim of minimizing selection bias and ensuring the standardization and reliability of the data obtained. Nonetheless, information bias was acknowledged as a possibility due to the heterogeneity of electronic medical record entries, particularly those concerning disease staging and the presence of metastases.

Data were tabulated using Microsoft Excel® for Microsoft 365 MSO (Version 2305 Build 16.0.16501.20074) and subjected to descriptive analysis. Absolute and relative frequencies of interactions classified as moderate and major were determined, in addition to the distribution of pharmacological mechanisms involved and the main potential clinical effects. The results are presented in Tables 1 and 2.

Table 1. Sociodemographic and Clinical Characteristics of the Sample (N = 232)

Characteristics	Values	
Age (years, mean)	65.5	
Sex	**%**	**n**
Female	74.5	173
Male	25.4	59
Types of solid neoplasms	**%**	**n**
Breast cancer	68.5	159
Prostate cancer	19.8	46
Colorectal cancer	6.9	16
Endometrial cancer	1.7	04
Others	3.0	07
Most prevalent comorbidities	**%**	**n**
Systemic arterial hypertension	63.8	148
Diabetes mellitus	29.7	69
Dyslipidemia	18.5	43
Obesity	5.6	13
Thyroid disorders	5.6	13
Depression	4.3	10
Osteoporosis	4.3	10
Pharmacotherapy	**%**	**n**
Frequency of polypharmacy	59.0	137
Frequency of drug interactions	23.3	54

Results

A total of 581 medical records were considered eligible for investigation. After applying the exclusion criteria defined in the methodology, 232 records were ultimately included in the analysis, as shown in the methodological flowchart (Figure 1).

More than half (65.1%) of the participants were older adults (≥ 60 years), with a mean age of 65.5 years. Regarding sex, 74.5% (n = 173) were female, and 25.4% (n = 59) were male. The patients were using one of the following oral antineoplastic agents: tamoxifen (TMX), anastrozole, cyclophosphamide, exemestane, vinorelbine, capecitabine, and bicalutamide.

With respect to the clinical profile of the patients, all had diagnoses of solid tumors, with the most frequent classifications being: breast cancer (68.5%), prostate cancer (19.8%), colorectal cancer (6.9%), endometrial cancer (1.7%), and others (3.0%).

The most frequently recorded comorbidities in the medical records were systemic arterial hypertension (63.8%), diabetes mellitus (29.7%), dyslipidemia (18.5%), thyroid disorders (5.6%), obesity (5.6%), depression (4.3%), and osteoporosis (4.3%). The majority of patients (59%) were using four or more medications, thus meeting the criteria for polypharmacy.

In this study, drug interactions were identified in the pharmacotherapy of 23.3% (n = 54) of the medical records included, representing an absolute frequency of 63 drug interactions involving the aforementioned oral antineoplastic agents.

Table 2. Description of Potentially Undesirable Drug Interactions Involving Oral Antineoplastic Agents

Interaction	Clinical effect	Severity	Mechanism	Absolute frequency	Relative frequency (%)
Bicalutamide + simvastatin	Increased risk of hepatotoxicity and rhabdomyolysis	Moderate	Pharmacokinetic	13	20.6
Capecitabine + hydrochlorothiazide	Prolonged bone marrow suppression	Moderate	Unknown	09	14.2
Tamoxifen + duloxetine	Reduced serum endoxifen levels	Major	Pharmacodynamic	05	7.9
Tamoxifen + escitalopram	QTc interval prolongation	Moderate	Pharmacodynamic	04	6.3
Tamoxifen + venlafaxine	QTc interval prolongation	Moderate	Pharmacodynamic	03	4.6
Tamoxifen + amitriptyline	QTc interval prolongation	Moderate	Pharmacodynamic	02	3.1
Capecitabine + pantoprazole	Reduced antineoplastic absorption	Moderate	Pharmacokinetic	02	3.1
Bicalutamide + cilostazol	Increased plasma levels of cilostazol	Moderate	Pharmacokinetic	02	3.1
Tamoxifen + trazodone	QTc interval prolongation	Moderate	Pharmacodynamic	01	1.5
Tamoxifen + hydroxychloroquine	QTc interval prolongation	Major	Pharmacodynamic	01	1.5
Tamoxifen + ciprofloxacin	QTc interval prolongation	Moderate	Pharmacodynamic	01	1.5
Tamoxifen + paroxetine	Reduced serum endoxifen levels	Moderate	Pharmacokinetic	01	1.5
Tamoxifen + dexamethasone	Reduced serum endoxifen levels	Moderate	Pharmacokinetic	01	1.5
Tamoxifen + risperidone	QTc interval prolongation	Moderate	Pharmacodynamic	01	1.5
Tamoxifen + mirtazapine	QTc interval prolongation	Moderate	Pharmacodynamic	01	1.5
Tamoxifen + sertraline	Reduced serum endoxifen levels	Major	Pharmacokinetic	01	1.5
Tamoxifen + fluoxetine	Reduced serum endoxifen levels	Major	Pharmacokinetic	01	1.5
Tamoxifen + fluconazole	QTc interval prolongation	Moderate	Pharmacodynamic	01	1.5
Cyclophosphamide + cyclosporine	Reduced serum cyclosporine levels	Moderate	Unknown	01	1.5
Exemestane + dexamethasone	Reduced serum exemestane levels	Moderate	Pharmacokinetic	01	1.5
Vinorelbine + carbamazepine	Reduced plasma vinorelbine levels	Moderate	Pharmacokinetic	01	1.5
Vinorelbine + rosuvastatin	Increased risk of neuropathy	Moderate	Pharmacodynamic	01	1.5
Vinorelbine + dexamethasone	Reduced serum vinorelbine levels	Moderate	Pharmacokinetic	01	1.5
Capecitabine + chlorthalidone	Prolonged bone marrow suppression	Moderate	Unknown	01	1.5
Bicalutamide + amitriptyline	QTc interval prolongation	Moderate	Pharmacodynamic	01	1.5
Bicalutamide + methotrexate	Increased risk of hepatotoxicity	Moderate	Pharmacokinetic	01	1.5
Bicalutamide + quetiapine	Increased serum quetiapine levels	Moderate	Pharmacokinetic	01	1.5
Bicalutamide + tramadol	QTc interval prolongation	Moderate	Pharmacokinetic	01	1.5
Bicalutamide + escitalopram	QTc interval prolongation	Moderate	Pharmacodynamic	01	1.5
Bicalutamide + mirabegron	Increased serum mirabegron levels	Minor	Pharmacokinetic	01	1.5
Bicalutamide + nortriptyline	QTc interval prolongation	Moderate	Pharmacodynamic	01	1.5
Total				63	100

*TMX = Tamoxifen. †QTc = Cardiac QT interval.

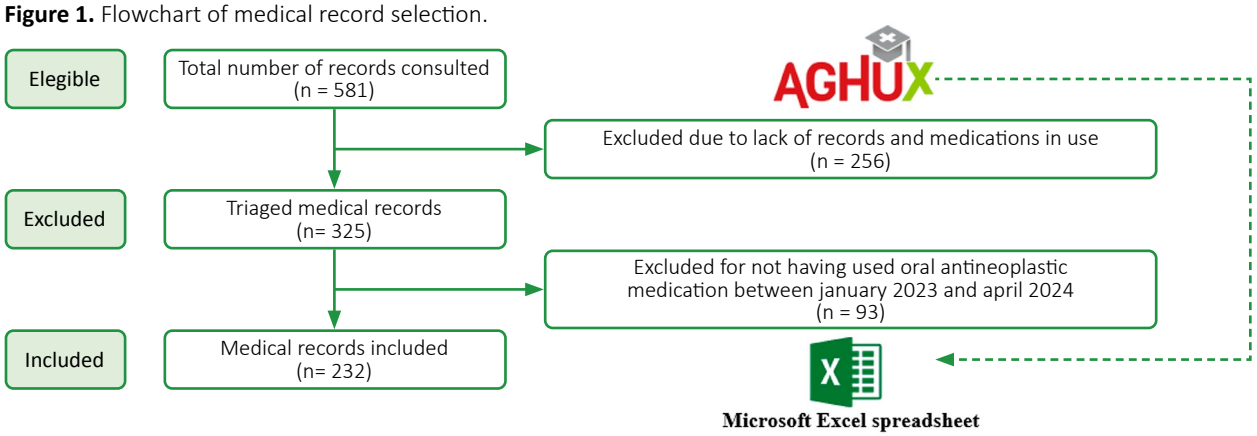
In total, 31 distinct types of drug interactions were identified, along with their potential undesirable clinical effects and their absolute and relative frequencies (Table 1).

It was also observed that the antineoplastic agents most frequently involved in drug interactions were tamoxifen and bicalutamide, accounting for 38.0% and 35.0%, respectively, of the identified interactions. Among the non-antineoplastic drugs most frequently involved in interactions, the most common were simvastatin, hydrochlorothiazide, and duloxetine, representing 20.6% (n = 13), 14.2% (n = 9), and 7.9% (n = 5), respectively. Regarding the severity of the interactions, 16.1% (n = 5) were classified as major/severe, 80% (n = 25) as moderate, and 3.2% (n = 1) as minor.

As for the pharmacological mechanisms, just over half of the interactions (51.6%) were pharmacodynamic, while 38.7% were pharmacokinetic, and 9.7% involved unknown mechanisms. Among all identified drug interactions, approximately 48.0% (n = 15) had the potential to prolong the cardiac QT interval (QTc), and about 32.0% (n = 10) could lead to a reduction in the efficacy of one of the oral antineoplastic agents.

It is noteworthy that the majority of drug interactions in patients using tamoxifen for breast cancer treatment involved antidepressant drugs, whose combination may lead either to a reduction in serum levels of tamoxifen's active metabolite (endoxifen) or to QTc interval prolongation (Table 2). Among these antidepressants, the most frequent was duloxetine (7.9%), followed by escitalopram (6.3%), venlafaxine (4.6%), and amitriptyline (3.1%). These drugs are commonly prescribed to alleviate tamoxifen-related side effects, particularly hot flashes, as well as to manage depressive mood disorders.

Figure 1. Flowchart of medical record selection.



AGHUx = Management Application for University Hospitals.

Discussion

In the present study, the frequency of drug interactions was relatively low, affecting approximately one-fourth of the sample of oncology patients undergoing treatment with oral antineoplastic agents. It is important to highlight that the frequency of identified interactions was significantly influenced by the exclusion of medical records that lacked information on patients' current medications. This limitation likely reduced the number of eligible records that could have contributed to a larger and potentially more representative sample for detecting possible interactions. Nevertheless, the results obtained allowed for clinically relevant interpretations.

It is well established that endoxifen (4-hydroxy-N-desmethyl-tamoxifen) is the main active metabolite of tamoxifen, and that its hepatic biotransformation is primarily mediated by the CYP2D6 enzyme, and to a lesser extent, by CYP3A4[9]. Among the drugs most implicated in this type of pharmacokinetic interaction with tamoxifen are the selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), which are recognized CYP2D6 inhibitors[10]. Therefore, theoretically, the efficacy of tamoxifen may be affected by the concomitant use of CYP2D6 inhibitors due to reduced exposure to endoxifen.

Drugs that inhibit this CYP isoenzyme could, in theory, reduce the metabolic activation of tamoxifen. Examples of strong CYP2D6 inhibitors include amitriptyline, fluoxetine, and paroxetine; moderate inhibitors include bupropion, duloxetine, and sertraline; and weak inhibitors include citalopram, escitalopram, venlafaxine, desvenlafaxine, and fluvoxamine[11]. Therefore, there is biological plausibility to support avoiding the combination of tamoxifen with CYP2D6 inhibitors, as such interactions result in a reduction in the formation of its active metabolite[12].

However, some published studies question whether this interaction between antidepressants and tamoxifen translates into an increased risk of breast cancer recurrence. For example, a cohort study including 16,887 women using antidepressants and 2,946 women who developed breast cancer over a 14-year period found no statistically significant increase in breast cancer risk among women who used paroxetine concurrently with tamoxifen[13].

These findings suggest that, although there is pharmacological rationale for caution, the clinical relevance of the interaction between tamoxifen and CYP2D6 inhibitors remains a matter of debate in the literature.

Nearly half of the drug interactions identified in this study had the potential to prolong the QTc interval, which is considered prolonged when it exceeds 470 ms in women and 450 ms in men[14]. This prolonged repolarization increases the risk of triggering torsades de pointes (TdP)—a form of polymorphic ventricular tachycardia that can lead to ventricular fibrillation and sudden cardiac death[15].

Pharmacotherapy, beyond the clinical event of the interaction itself, is an important cause of QTc prolongation. Although some interactions may be associated with this serious adverse effect, there is limited evidence supporting the clinically significant frequency of long QTc syndrome, considering the risk as only potential, while the benefit of therapy may, in some cases, outweigh the supposed risk.[16] The drugs identified in this study that increase the risk of QTc interval prolongation—either individually or, more importantly, when co-administered with TMX—include SSRIs, amitriptyline, venlafaxine, trazodone, mirtazapine, hydroxychloroquine, and ciprofloxacin.

Indeed, both TMX and SSRIs can independently prolong the QTc interval, and their combined use may result in an increased risk of this adverse effect. The risk of QTc prolongation in breast cancer patients treated with TMX and SSRIs may lead to an average increase of 12.4 ms relative to the upper physiological QTc limit, being more pronounced with paroxetine, escitalopram, and citalopram, although not exceeding 500 ms.[17] This risk should be taken into account, as SSRIs are frequently used in the oncology population for the management of depression, which increases the likelihood of this interaction occurring.

A prospective cohort study showed that androgen deprivation therapy (ADT) is associated with QTc prolongation of 7.4 ms (95% confidence interval 0.08–14.7; p = 0.048) compared to those not receiving such therapy.[18] The biological effect of testosterone is inversely associated with QTc duration, given its physiological role in maintaining ventricular repolarization in male patients.[19]

Thus, it is plausible that reduced testosterone activity (male hypogonadism), including during ADT use, is associated with QTc prolongation. Another prospective cohort also concluded that ADT may act as a risk factor for QTc prolongation and, consequently, an increased risk of torsades de pointes (TdP).

Patients with prostate cancer are at high risk for potential drug–drug interactions. Among pharmacodynamic interaction outcomes, the combination of two or more drugs that prolong the QTc interval stands out, resulting in additive or synergistic effects. It is known that ADT has been associated with QTc prolongation.[18] Moreover, TMX also blocks the potassium channel that regulates repolarizing currents (Ikr), which can likewise prolong the QTc interval.[20]

Drugs that prolong the QTc interval are classified according to their risk of inducing TdP into three categories: "known," "possible," or "conditional." The "known" category refers to drugs with substantial evidence of association with TdP; "possible" applies when there is evidence of QTc prolongation but no clear demonstration of TdP risk; and "conditional" refers to drugs whose TdP risk depends on specific conditions, such as high doses, drug interactions, or individual predisposition.[21] Accordingly, escitalopram and citalopram are classified as having a known risk of QTc prolongation; venlafaxine, imipramine, nortriptyline, and tamoxifen as possible risk; and paroxetine, amitriptyline, sertraline, and fluoxetine as conditional risk.[17]

Bicalutamide belongs to the first generation of nonsteroidal antiandrogenic antineoplastic agents. Although limited, there is evidence in the literature that this drug may prolong the QTc interval due to its antiandrogenic effect. Therefore, concomitant use with other QTc-prolonging drugs may result in additive or synergistic effects through a pharmacodynamic mechanism. In the analyzed sample, examples of such drugs whose interaction with bicalutamide was identified include tricyclic antidepressants (amitriptyline, nortriptyline), tramadol, and escitalopram.

Nonetheless, it is important to consider other factors beyond medication use alone that contribute to QTc prolongation. These include intrinsic patient characteristics such as age > 65 years, female sex, congenital long QT syndrome, the degree of QT interval prolongation associated with the drug, and, evidently, the presence of pharmacokinetic and pharmacodynamic interactions that may further increase the risk of prolongation.[15] Moreover, despite the clinical relevance of this event, there is a scarcity of robust clinical data in the literature that directly quantify mortality attributable solely to such drug interactions.

The occurrence of drug–drug interactions was directly associated with the number of concomitant medications. In this regard, more than half (59%) of the patients were undergoing polypharmacy. This finding is consistent with available literature, as polypharmacy is one of the most common variables associated with adverse clinical events in older adults with cancer and is a significant independent predictor of harm.[22,23] It is worth noting that the mean age of the study sample was 65.5 years. Indeed, these patients are more likely to present with frailty, comorbidities, and geriatric syndromes than non-oncologic older adults, placing the oncogeriatric population at high risk for adverse events secondary to potential unwanted interactions.

The most frequently observed interaction in the analyzed sample was the concomitant use of bicalutamide and simvastatin (Table 2). Acute liver injury induced by bicalutamide, although rare, has been reported in the literature.[24]Statins can induce increases in aminotransferase levels, which are self-limiting upon drug discontinuation, suggesting hepatocellular injury, particularly at higher doses.[25,26] Only 3% of patients presented aminotransferase elevations greater than three times the upper limit of normality.[27]

Furthermore, *in vitro* data suggest that the (R)-bicalutamide enantiomer has the potential to inhibit CYP3A4 and, therefore, could theoretically increase the concentrations of HMG-CoA reductase inhibitors (statins) metabolized by this cytochrome P450 enzyme.[27] However, no published studies have evaluated the clinical significance of this potential interaction between statins and bicalutamide. Therefore, the fact that this was identified as a potential and frequent drug–drug interaction in the studied sample does not necessarily imply that it has clinically significant impact.

Among the identified interactions, some did not present known pharmacological mechanisms described in the available literature (Table 2). One example is the supposed effect of thiazide diuretics (hydrochlorothiazide and chlorthalidone) in prolonging capecitabine-induced bone marrow suppression. Another example is the coadministration of cyclophosphamide and cyclosporine, in which the former reduces the plasma concentration of the latter.

Through distinct mechanisms of action, vinorelbine and statins may cause peripheral neuropathy. Chemotherapy agents targeting microtubules, such as vinca alkaloids, have peripheral neuropathy as a prominent side effect, although its pathogenesis is not fully understood.[28] In clinical practice, patients are often exposed to combinations of drugs that, even when administered individually, can cause peripheral neuropathy. A notable example is the class of HMG-CoA reductase inhibitors (statins), one of the most frequently prescribed drug groups, whose prolonged use may lead to peripheral neuropathy. The pathogenesis of this adverse effect associated with statin therapy also remains unclear.[29]

There is, in fact, evidence that proton pump inhibitors (PPIs) may reduce the efficacy of capecitabine through a recognized pharmacokinetic mechanism. Although, in this study, the frequency of interactions involving PPI use among patients treated with capecitabine was low (3.1%), their clinical significance is noteworthy. Several studies on colorectal cancer (CRC) have demonstrated shorter progression-free and overall survival in patients treated with capecitabine concomitantly with PPIs compared to those receiving capecitabine monotherapy or intravenous 5-fluorouracil (5-FU)—its active metabolite.

Different studies have investigated the impact of PPIs on the pharmacokinetics and efficacy of capecitabine. A retrospective study including 298 eligible patients with early-stage (I–III) CRC treated with adjuvant capecitabine monotherapy found a statistically significant reduction in 5-year recurrence-free survival among those receiving PPIs compared to nonusers.[30] Another retrospective cohort including 70 patients demonstrated that gastric acid suppression during capecitabine therapy was associated with decreased progression-free survival and a numerical reduction in overall survival compared with patients not receiving acid-suppressive therapy.[31]

Furthermore, two additional studies compared the influence of PPIs on the efficacy of oral capecitabine and intravenous 5-fluorouracil. The first, a retrospective cohort study of 389 patients with stage II–III CRC who received either CapeOx (capecitabine plus intravenous oxaliplatin) or FOLFOX (intravenous 5-FU, leucovorin, and oxaliplatin) as adjuvant therapy, demonstrated that PPIs negatively affected recurrence-free survival in patients treated with CapeOx but had no significant impact on those treated with FOLFOX.[32]

A post hoc analysis of a randomized clinical trial also identified a significant interaction between PPI use and mXELIRI (capecitabine plus irinotecan), showing worse progression-free and overall survival compared with patients treated with FOLFIRI (leucovorin, intravenous 5-FU, and irinotecan) who were taking PPIs.[33] Taken together, these studies suggest that the interaction between PPIs and capecitabine is clinically significant, negatively impacting the chemotherapeutic efficacy of capecitabine—particularly due to the well-established pharmacokinetic mechanism underlying this interaction.

Ultimately, this study presents some limitations that should be considered when interpreting the results. The data were obtained from a single sample within a specific hospital service, which may limit the generalizability of the findings to other healthcare settings—particularly given potential variations in treatment protocols, patient profiles, and drug–drug interaction monitoring systems implemented by individual clinical and oncology pharmacy services.

Furthermore, the cross-sectional design does not allow for establishing causal relationships between the analyzed variables. Another limitation concerns the possible underreporting of drug interactions, since the study relied exclusively on clinical records and electronic prescription data available in the medical charts. Finally, it is important to emphasize that adverse clinical outcomes potentially related to the identified drug interactions were not observed within the clinical setting where data collection was conducted. This is attributable both to the methodological approach and study objectives, as well as to the fact that the clinical repercussions of these interactions are theoretically presumed based on existing scientific evidence.

Conclusion

The frequency of potential drug–drug interactions (DDIs) among oncology patients undergoing oral antineoplastic therapy was low. However, the medical records included in this study represented less than half of all initially eligible charts, since the majority were excluded due to a lack of information regarding concomitant medication use. On the other hand, the analyzed sample exhibited a high prevalence of risk factors, such as polypharmacy, multiple comorbidities, and a predominance of older adults, all of which are closely associated with an increased likelihood of undesirable effects related to DDIs.

The identified interactions mainly involved commonly prescribed antidepressants, whose concomitant use with antineoplastic agents such as tamoxifen or bicalutamide increases the risk of QTc interval prolongation through distinct mechanisms. Although this adverse effect is theoretically presumed, it should not be disregarded in clinical practice, as QTc prolongation is strongly associated with malignant arrhythmias and sudden cardiac death. Other potential undesirable outcomes identified—such as myelosuppression, hepatotoxicity, neuropathy, and reduced serum concentrations of tamoxifen's active metabolite—also warrant close attention from clinical pharmacists and prescribers.

Despite these possible and theoretical repercussions associated with the identified DDIs, the risk–benefit balance must always be considered during outpatient follow-up. Ultimately, knowledge of such interactions primarily aims to support clinicians in the decision-making process when faced with potentially adverse pharmacological effects. This awareness can help minimize unwanted clinical outcomes, thereby optimizing oncologic therapy and promoting safer prescribing practices—contributing to overall quality and safety in oncologic care.

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Contributors

Study conception and design, data analysis and interpretation: Silva HD, Júnior, LA.

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Conflict of Interest Statement

The authors declare no conflicts of interest related to this work.

References

1. World Health Organization. Medication without harm: policy brief. Geneva: WHO; 2023.
2. Kim SH, Suh Y, Ah YM, et al. Real-world prevalence of potential drug-drug interactions involving oral antineoplastic agents: a population-based study. Support Care Cancer. 2020;28(8):3617-3626. doi:10.1007/s00520-019-05204-2
3. Mousavi S, Ghanbari G. Potential drug-drug interactions among hospitalized patients in a developing country. Caspian J Intern Med. 2017;8(4):282-288. doi:10.22088/cjim.8.4.282
4. World Health Organization. Reporting and learning systems for medication errors: the role of pharmacovigilance centres. Geneva: WHO; 2014.
5. Scripture CD, Figg WD. Drug interactions in cancer therapy. Nat Rev Cancer. 2006;6(7):546-558. doi:10.1038/nrc1887
6. Katzung B. G. e Vanderah, T. W. Farmacologia Básica e Clínica. Porto Alegre: AMGH, 2022.
7. Leal KD, Leopoldino RW, Martins RR, et al. Potential intravenous drug incompatibilities in a pediatric unit. Einstein. 2016;14(2):185-189. doi:10.1590/S1679-45082016AO3723

8. Rezende LFM, Lee DH, Louzada MLDC, et al. Proportion of cancer cases and deaths attributable to lifestyle risk factors in Brazil. Cancer Epidemiol. 2019;59:148-157. doi:10.1016/j.canep.2019.01.021

9 Hansten PD. The Underrated Risks of Tamoxifen Drug Interactions. Eur J Drug Metab Pharmacokinet. 2018;43(5):495-508. doi:10.1007/s13318-018-0475-9

10. Sanchez-Spitman AB, Swen JJ, Dezentje VO, et al. Clinical pharmacokinetics and pharmacogenetics of tamoxifen and endoxifen. Expert Rev Clin Pharmacol. 2019;12(6):523-536. doi:10.1080/17512433.2019.1610390

11. Irarrázaval O ME, Gaete G L. Elección del mejor antidepresivo en pacientes con cáncer de mama en tratamiento con tamoxifeno: revisión de la evidencia básica y clínica. Rev Med Chil. 2016;144(10):1326-1335. doi:10.4067/S0034-98872016001000013

12. Van Leeuwen RWF, le Comte M, Reyners AKL, et al. Evidence- and consensusbased guidelines for drug-drug interactions with anticancer drugs; A practical and universal tool for management. Semin Oncol. 2022;49(2):119-129. doi:10.1053/j.seminoncol.2022.03.002

13. Haque R, Shi J, Schottinger JE, et al. Tamoxifen and Antidepressant Drug Interaction in a Cohort of 16,887 Breast Cancer Survivors. J Natl Cancer Inst. 2015;108(3):djv337. doi:10.1093/jnci/djv337

14. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793-2867. doi:10.1093/eurheartj/ehv316

15. Khatib R, Sabir FRN, Omari C, et al. Managing drug-induced QT prolongation in clinical practice. Postgrad Med J. 2021;97(1149):452-458. doi:10.1136/postgradmedj-2020-138661

16. Armahizer MJ, Seybert AL, Smithburger PL, et al. Drug-drug interactions contributing to QT prolongation in cardiac intensive care units. J Crit Care. 2013;28(3):243-249. doi:10.1016/j.jcrc.2012.10.014

17. Hussaarts KGAM, Berger FA, Binkhorst L, et al. The Risk of QTc-Interval Prolongation in Breast Cancer Patients Treated with Tamoxifen in Combination with Serotonin Reuptake Inhibitors. Pharm Res. 2019;37(1):7. doi:10.1007/s11095-019-2746-9

18. Gagliano-Jucá T, Travison TG, Kantoff PW, et al. Androgen Deprivation Therapy Is Associated With Prolongation of QTc Interval in Men With Prostate Cancer. J Endocr Soc. 2018;2(5):485-496. doi:10.1210/js.2018-00039

19. Salem JE, Alexandre J, Bachelot A, et al. Influence of steroid hormones on ventricular repolarization. Pharmacol Ther. 2016;167:38-47. doi:10.1016/j.pharmthera.2016.07.005

20. Grouthier V, Lebrun-Vignes B, Glazer AM, et al. Increased long QT and torsade de pointes reporting on tamoxifen compared with aromatase inhibitors. Heart. 2018;104(22):1859-1863. doi:10.1136/heartjnl-2017-312934

21. Schwartz PJ, Woosley RL. Predicting the Unpredictable: Drug-Induced QT Prolongation and Torsades de Pointes. J Am Coll Cardiol. 2016;67(13):1639-1650. doi:10.1016/j.jacc.2015.12.063

22. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015;175(5):827-834. doi:10.1001/jamainternmed.2015.0324

23. Ramsdale E, Mohamed M, Yu V, et al. Polypharmacy, Potentially Inappropriate Medications, and Drug-Drug Interactions in Vulnerable Older Adults With Advanced Cancer Initiating Cancer Treatment. Oncologist. 2022;27(7):e580-e588. doi:10.1093/oncolo/oyac053

24. Hussain S, Haidar A, Bloom RE, et al. Bicalutamideinduced hepatotoxicity: A rare adverse effect. Am J Case Rep. 2014;15:266-270. doi:10.12659/AJCR.890679

25. Karahalil B, Hare E, Koç G, et al. Hepatotoxicity associated with statins. Arh Hig Rada Toksikol. 2017;68(4):254-260. doi:10.1515/aiht-2017-68-2994

26. Averbukh LD, Turshudzhyan A, Wu DC, et al. Statin-induced Liver Injury Patterns: A Clinical Review. J Clin Transl Hepatol. 2022;10(3):543-552. doi:10.14218/JCTH.2021.00271

27. Cockshott ID. Bicalutamide: clinical pharmacokinetics and metabolism. Clin Pharmacokinet. 2004;43(13):855-878. doi:10.2165/00003088-200443130-00003

28. Brewer JR, Morrison G, Dolan ME, et al. Chemotherapy-induced peripheral neuropathy: Current status and progress. Gynecol Oncol. 2016;140(1):176-183. doi:10.1016/j.ygyno.2015.11.011

29. Gaist D, Jeppesen U, Andersen M, et al. Statins and risk of polyneuropathy: a case-control study. Neurology. 2002;58(9):1333-1337. doi:10.1212/wnl.58.9.1333

30. Sun J, Ilich AI, Kim CA, et al. Concomitant Administration of Proton Pump Inhibitors and Capecitabine is Associated With Increased Recurrence Risk in Early Stage Colorectal Cancer Patients. Clin Colorectal Cancer. 2016;15(3):257-263. doi:10.1016/j.clcc.2015.12.008

31. Rhinehart HE, Phillips MA, Wade N, et al. Evaluation of the clinical impact of concomitant acid suppression therapy in colorectal cancer patients treated with capecitabine monotherapy. J Oncol Pharm Pract. 2019;25(8):1839-1845. doi:10.1177/1078155218818237

32. Wong GG, Ha V, Chu MP, et al. Effects of Proton Pump Inhibitors on FOLFOX and CapeOx Regimens in Colorectal Cancer. Clin Colorectal Cancer. 2019;18(1):72-79. doi:10.1016/j.clcc.2018.11.001

33. Kim SY, Lee JS, Kang J, et al. Proton Pump Inhibitor Use and the Efficacy of Chemotherapy in Metastatic Colorectal Cancer: A Post Hoc Analysis of a Randomized Phase III Trial (AXEPT). Oncologist. 2021;26(6):e954-e962. doi:10.1002/onco.13735