DRUG INTERACTION IN BREAST CANCER PATIENTS

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ABSTRACT

Breast cancer is developed due to abnormal cell proliferation that turns it into a tumor with metastasis potential. This cancer occurs mainly in women, only 1% of breast cancer's cases in Brazil is in men. Breast cancer is the main cause of women death in Brazil. The treatment for this cancer includes chemotherapy, hormonotherapy and/or targeted therapy, but it also includes others drugs to reduce side-effects as well as treating comorbidities. Thus, oncologic patients have a high risk of drug interaction and they need a multiprofessional team to ensure drug safety and efficiency. Therefore, this work aimed to analyze drugs interactions in breast cancer patients in use of antitumor drugs. A qualitative analysis was carried out by collecting data from medical records of patients with breast cancer treated at a philantroc hospital in Espírito Santo between the years 2012 and 2022. The main interactions identified were the association of doxorubicin with docetaxel or trastuzumab. Despite the large number of expected interactions, the number of team interventions was small, showing that the role of the pharmacist can be crucial for improving the quality of life of breast cancer patients.

Keywords: *Drug interaction. Breast Cancer. Antitumor drugs. Drugs.*

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1 INTRODUCTION

Breast cancer is the cancer with the highest incidence among women in Brazil. It should be noted that this cancer also affects men, but it represents only 1% of total cases. According to the National Cancer Institute (INCA), an estimated 73,610 new cases are projected for the 2023–2025 period. Additionally, in 2019, there were 18,295 deaths, with women accounting for 18,068 cases and men for 227 (INCA, 2022).

Breast cancer can be defined as a set of diseases caused by the disorganized replication of abnormal breast cells, which develop into a tumor with the possibility of metastasis. These tumors can be classified, according to their molecular markers, into: luminal A, luminal B, HER2+ and triple negative (Tan *et al.*, 2020). Although the main risk factor for the development of this cancer is aging, it is noteworthy that other factors are involved such as: early menarche, nulliparity, age at first full-term pregnancy over 30 years old, use of oral contraceptives, late menopause and use of hormone replacement therapy (INCA, 2022).

Breast cancer treatment depends on the stage and type of tumor. When the disease is diagnosed early, treatment has greater curative potential. In the case of metastatic disease, treatment seeks to prolong survival and improve quality of life. Therapeutic options include surgery, radiotherapy, chemotherapy, hormonotherapy and targeted therapy (Cardoso *et al.*, 2020).

In a drug treatment, such as chemotherapy, hormone therapy and targeted anticancer therapy, it is the duty of the multidisciplinary team to ensure that there is no interaction between the drugs used by patients. Drug interaction is defined as the pharmacological, toxicological, clinical or laboratory response caused by the combination of medications. It can also arise from the interaction of the medicine combined with food, chemical substances or illnesses. As a consequence, the results of laboratory tests may have their guarantee damaged, resulting in an increase or decrease in therapeutic effectiveness or even the appearance of new adverse effects (Masnoon *et al.*, 2017).

Among the medications available for the treatment of breast cancer, there is a high incidence of drug interactions, compromising the effectiveness and availability of medications and/or triggering toxic effects. Among some of the medications prescribed for breast cancer treatment, we can mention some, for example, capecitabine, tamoxifen, cyclosphosphamide and gemcitabine (Alves; Tavares; Borges, 2020).

Capecitabine may be related to six interactions with diseases, namely infections, coronary artery disease, myelosuppression, renal dysfunction, dehydration and liver dysfunction. Tamoxifen has 460 drug interactions, 132 of which are serious interactions, such as that resulting from its association with escitalopram. Cyclophosphamide has 347 drug interactions, but only 54 are serious. As for gemcitabine, 232 medications are known to interact with it, categorized as 41 major interactions, 173 moderate interactions and 18 minor interactions (Drugs, 2024).

In this way, the pharmacist within the oncology sector plays an extremely important role. The pharmacist is responsible for monitoring all drug therapy, ensuring that it is appropriate for the patient, thus providing a better quality of life and treatment effectiveness. Furthermore, it helps to reduce medication errors in prescriptions and helps to observe adverse effects that may result from the combined use of medications, especially in cancer patients, where the number of drugs used is high (Alves; Tavares; Borges, 2020). Therefore, given the impact of drug interactions on the oncology service, this study evaluated drug interactions in patients with breast cancer treated at a philanthropic hospital in Espírito Santo.

2 MATERIAL AND METHODS

After approval by the Human Research Ethics Committee of the Centro Universitário do Espírito Santo (CEP UNESC) (opinion number 5.656.342 and Certificate of Presentation of Ethical Appreciation, CAAE, number 63059022.9.0000.5062), the character research began. Data collection was carried out through medical records of patients with breast cancer treated at a philanthropic hospital in Espírito Santo between 2012 and 2022 present in the Soul-mv hospital management system, in which they were observed (gender, age, tumor type, medications, dose used and notification of adverse effects). The analysis of predicted drug interactions was based on data from the electronic platforms “drugs.com” and “Lexicomp® DrugInteractions” from “©UpToDate” from the company WoltersKluwer N.V.

3 RESULTS

In this work, 100 patients diagnosed with primary breast cancer and treated at the hospital oncology care service between the years 2012 and 2022 were randomly selected. The analysis of these patients' medical records included evaluation throughout their successive visits to the various health services of this institution.

Regarding the characterization of the studied population (Table I), the population was composed only by women, mostly aged 61 years or over. The youngest patient included was 33 years old and the oldest patient was 89 years old. The main subtypes of breast cancer found were: ductal carcinoma *in situ* and invasive ductal carcinoma.

Table I - Characteristics of the studied population (n=100).

Characteristic		**n (%)**
Gender	Female	100 (100%)
	Male	0 (0%)
Age	18 to 40	5 (5%)
	41 to 60	43 (43%)
	61 or more	52 (52%)

Source: The Authors (2024)

Only one patient analyzed received intervention related to drug interaction (Table 2). This was the observation of grade 1 toxicity to taxane according to the “Common Terminology Criteria for Adverse Events” of the National Cancer Institute (NCI) of the United States of America.

Regarding the number of drugs described in the medical records, 26 patients used four medications or less and 74 used at least five drugs. The patient that used less medication were the one that used two drugs and the one that used more drugs associated were the one that used 15 drugs in a therapy. The most common predicted interactions were between doxorubicin and taxanes (in 58 patients) or trastuzumab (in

16 patients), both related to the increased risk of cardiotoxicity (Table II). Only 20 of the records did not present any type of predicted risk of interaction.

Table II – Evaluation of drugs and drug interactions in the studied population (n=100)

Pacient number	Prescribed drugs	Toxicity reported	What kind of toxicity?	Predicted drug interaction	Risk rating
1.	Anastrozole, clonazepam, doxorubicin, docetaxel and losartan	No	—	Doxorubicin and docetaxel	Moderate
2.	Fluoxetine, anastrozole, doxorubicin, clonazepam, losartan and ciprofibrate	No	—	Fluoxetine and clonazepam	Minor
3.	Captopril, hydrochlorothiazide, doxorubicin, docetaxel and alendronate	No	—	Captopril and hydrochlorothiazide; Doxorubicin and docetaxel	Moderate; Moderate
4.	Losartan, anastrozole, doxorubicin and trastuzumab	No	—	Doxorubicin and trastuzumab	Major
5.	Tamoxifen, doxorubicin and medroxyprogesterone	No	—	—	—
6.	Doxorubicin, amlodipine, simvastatin, trastuzumab and NPH insulin	No	—	Amlodipine and simvastatin	Moderate
7.	Losartan, amlodipine, atenolol, diosmin, hesperidin, hydrochlorothiazide, metoprolol, citalopram, rivaroxaban, paclitaxel, doxorubicin, pantoprazole and atorvastatin	No	—	Citalopram and rivaroxaban	Moderate
8.	Docetaxel, tamoxifen, doxorubicin and cyclophosphamide	No	—	Docetaxel and doxorubicin	Moderate
9.	Tamoxifen, doxorubicin, cyclophosphamide and clonazepam	No	—	—	—
10.	Omeprazole, acetylsalicylic acid, losartan, metformin, simvastatin, folic acid,	No	—	Metformin and metoprolol	Moderate

	metoprolol and anastrozole				
11.	Capecitabine, doxorubicin, cyclophosphamide and docetaxel	No	—	Doxorubicin and docetaxel	Moderate
12.	Tamoxifen, doxorubicin, cyclophosphamide and docetaxel	No	—	Doxorubicin and docetaxel	Moderate
13.	Anastrozole, isosorbide mononitrate, metoprolol, simvastatin, losartan, clopidogrel, acetylsalicylic acid, metformin, gabapentin, amlodipine, bromazepam, carvedilol, NPH insulin, paclitaxel and trastuzumab	No	—	Clopidogrel and omeprazole; Simvastatin and amlodipine; Bromazepam and gabapentin; Clopidogrel and amlodipine; Insulin and carvedilol; Metformin and carvedilol; Clopidrogrel and simvastatin	Major; Moderate; Moderate; Minor; Moderate; Moderate; Minor
14.	Trastuzumab, anastrozole, doxorubicin and placitaxel	No	—	Trastuzumab and doxorubicin; Paclitaxel and doxorubicin	Major; Moderate; Moderate; Moderate; Moderate
15.	Metformin, acetylsalicylic acid, carvedilol, losartan, anastrozole, metoprolol and rosuvastatin	No	—	Carvedilol and metoprolol; Metformin and carvedilol; Metformin and metoprolol	Moderate; Moderate; Moderate
16.	Docetaxel, ciprofloxacin, dipyrone, paracetamol, tamoxifen, albendazole, cephalexin and paclitaxel	No	—	Tamoxifen and dipyrone	Moderate
17.	Tamoxifen, carvedilol, spironolactone, trastuzumab, azithromycin, fluconazole, paroxetine, enalapril, doxorubicin and cyclophosphamide	No	—	Tamoxifen and fluconazole; Tamoxifen and paroxetine; Trastuzumab and doxorubucin; Doxorubucin and carvedilol; Doxorubucin and fluconazole; Doxorubucin and paroxetine; Carvedilol and fluconazole; Carvedilol and paroxetine	Minor; Major; Major; Minor; Moderate; Moderate; Moderate; Moderate
18.	Gliclazide, losartan, propranolol,	No	—	—	—

	simvastatin and tamoxifen				
19.	Metformin, gliclazide, simvastatin, ciprofloxacin, valsartan, trastuzumab, anastrozole, docetaxel and doxorubicin	No	—	Doxorubicin and trastuzumab; Doxorubicin and docetaxel; Metformin and gliclazide	Major; Moderate
20.	Doxorubicin, cyclophosphamide, docetaxel, fulvestrant, anastrozole, amlodipine, hydrochlorothiazide and zoledronic acid	No	—	Doxorubicin and docetaxel	Moderate
21.	Hydrochlorothiazide, propranolol, propatilnitrate, nortriptyline and anastrozole	No	—	—	—
22.	Atenolol, losartan, amlodipine, tamoxifen, doxorubicin, cyclophosphamide, furosemide and enalapril	No	—	Amlodipine and furosemide; Enalapril and losartan; Atenolol and furosemide; Enalapril and furosemide; Losartan and furosemide	Moderate; Moderate; Moderate; Moderate; Moderate
23.	Losartan, simvastatin, alendronate, citalopram, cephalexin, anastrozole and amlodipine	No	—	Simvastatin and amlodipine	Moderate
24.	Atenolol, levothyroxine, clonazepam, anastrozole, rosuvastatin and spironolactone	No	—	—	—
25.	Spironolactone, losartan, metformin, furosemide, amlodipine, calcium carbonate and anastrozole	No	—	Amlodipine and furosemide; Losartan and furosemide; Metformin and furosemide	Moderate; Moderate; Moderate
26.	Clonazepam, losartan, trastuzumab, docetaxel, pregabalin, desvenlafaxine, tamoxifen, alprazolam, quetiapine and doxorubicin	No	—	Alprazolam and quetiapine; Alprazolam and pregabalin; Alprazolam and clonazepam; Doxorubicin and docetaxel	Moderate; Moderate; Moderate; Moderate
27.	Metformin, haloperidol,	No	—	Haloperidol and amitriptyline	Moderate

	amitriptyline, anastrozole, acetylsalicylic acid and simvastatin				
28.	Omeprazole, docetaxel, doxorubicin and cyclophosphamide	No	—	Docetaxel and doxorubicin	Moderate
29.	Amitriptyline, trastuzumab, diazepam, docetaxel, doxorubicin, cyclophosphamide and zolpidem	No	—	Diazepam and amitriptyline; Trastuzumab and docetaxel; Zolpidem and amitriptyline; Zolpidem and diazepam; Docetaxel and doxorubicin	Moderate; Major; Major; Major; Moderate
30.	Losartan, anastrozole, hydrochlorothiazide, doxorubicin and docetaxel	No	—	Doxorubicin and docetaxel	Moderate
31.	Docetaxel, tamoxifen, doxorubicin and cyclophosphamide	No	—	Doxorubicin and docetaxel	Moderate
32.	Doxorubicin, cyclophosphamide, docetaxel and trazodone	No	—	Doxorubicin and cyclophosphamide; doxorubicin and docetaxel	Major; Moderate
33.	Metoprolol, atenolol, hydrochlorothiazide, B complex, ferrous sulfate, zolpidem, tramadol, escitalopram, tamoxifen, docetaxel and doxorubicin	No	—	Doxorubicin and cyclophosphamide; doxorubicin and docetaxel	Major; Moderate
34.	Amitriptyline, flavonoid, trastuzumab, carvedilol, enalapril, furosemide, anastrozole, amiodarone, tamoxifen, phenazopyridine, doxorubicin and docetaxel	No	—	Doxorubicin and trastuzumab; Doxorubicin and cyclophosphamide; doxorubicin and docetaxel; Tamoxifen and anastrozole; doxorubicin and carvedilol; Carvedilol and furosemide; Enalapril and furosemide	Major; Major; Moderate; Moderate; Minor; Moderate; Moderate
35.	Atenolol, amlodipine, simvastatin, anastrozole, paroxetine and escitalopram	No	—	Paroxetine and escitalopram	Major
36.	Escitalopram, tamoxifen, sertraline, gabapentin, olanzapine,	No	—	Escitalopram and tamoxifen; Olanzapine and tamoxifen;	Minor; Minor; Moderate; Moderate

	cephalexin, trastuzumab, pertuzumab and docetaxel			Olanzapine and sertraline; escitalopram and olanzapine	
37.	Hydrochlorothiazide, anastrozole, captopril, furosemide, citalopram, paclitaxel, tamoxifen, docetaxel, fulvestrant and doxorubicin	No	—	Doxorubicin and docetaxel; anastrozole and tamoxifen; Captopril and furosemide	Moderate; Moderate; Moderate
38.	Losartan, hydrochlorothiazide, escitalopram, docetaxel, pacitaxel, trastuzumab and doxorubicin	No	—	Doxorubicin and docetaxel; Trastuzumab and doxorubicin	Moderate; Major
39.	Doxorubicin, cyclophosphamide, docetaxel and anastrozole	No	—	Doxorubicin and docetaxel	Moderate
40.	Escitalopram, tamoxifen, doxorubicin and docetaxel	No	—	Doxorubicin and docetaxel; Tamoxifen and escitalopram	Moderate; Minor
41.	Dexamethasone, tamoxifen, docetaxel and doxorubicin	No	—	—	—
42.	Losartan, clonazepam and anastrozole	No	—	—	—
43.	Rosuvastatin, tamoxifen, doxorubicin, docetaxel, atenolol and losartan	No	—	Doxorubicin and docetaxel	Moderate
44.	Losartan, atenolol, metformin, acetylsalicylic acid, anastrozole, fulvestrant, carboplatin, hydrochlorothiazide, doxorubicin and docetaxel	No	—	Docetaxel and carboplatin; docetaxel and doxorubicin	Major; Moderate
45.	Atenolol, sertraline, paracetamol, ibuprofen and Tamoxifen	No	—	Sertraline and ibuprofen; Atenolol and ibuprofen	Major; Moderate
46.	Metformin, acetylsalicylic acid, spironolactone, metoprolol, enalapril, furosemide, simvastatin, rivaroxaban, calcium, anastrozole and fluvestrant.	No	—	Metformin and metoprolol; Metformin and enalapril	Moderate; Moderate
47.	Amitriptyline, spironolactone, anastrozole,	No	—	Doxorubicin and docetaxel	Moderate

	doxorubicin and docetaxel				
48.	Atenolol, acetylsalicylic acid, spironolactone, simvastatin, ciprofibrate, metformin, omeprazole, doxorubicin, docetaxel and trastuzumab	No	—	Trastuzumab and doxorubicin; simvastatin and ciprofibrate; Metformin and atenolol; Doxorubicin and docetaxel	Major; Moderate; Moderate; Moderate
49.	Losartan, propranolol, rosuvastatin, anastrozole, docetaxel and doxorubicin	No	—	Doxorubicin and docetaxel	Moderate
50.	Fluoxetine, clonazepam, propranolol, doxorubicin, docetaxel and anastrozole	No	—	Fluoxetine and clonazepam; docetaxel and doxorubicin	Minor; Moderate
51.	Spironolactone, amitriptyline, anastrozole, docetaxel and doxorubicin	No	—	Doxorubicin and docetaxel	Moderate
52.	Tamoxifen, doxorubicin, docetaxel and trastuzumab	No	—	Doxorubicin and docetaxel; Doxorubicin and trastuzumab	Moderate; Major
53.	Rivaroxaban, metoprolol, pantoprazole, spironolactone, furosemide, doxorubicin, docetaxel, anastrozole and hydrochlorothiazide	No	—	Doxorubicin and docetaxel; metoprolol and furosemide	Moderate; Moderate
54.	Atenolol, nifedipine, ciprofibrate and tamoxifen	No	—	—	—
55.	Amiloride, metformin, simvastatin, gliclazide, collagen, doxorubicin, cephalexin, docetaxel, trastuzumab, anastrozole, paracetamol and ibuprofen	No	—	Metformin and cephalexin; Gliclazide and metformin; Doxorubicin and docetaxel; Doxorubicin and trastuzumab	Moderate; Moderate; Moderate; Major
56.	Gabapentin, losartan, anastrozole, doxorubicin and docetaxel	No	—	Doxorubicin and docetaxel	Moderate
57.	Diosmin, hesperidin, acetylsalicylic acid, omeprazole, levothyroxine, anastrozole and hydrochlorothiazide	No	—	Levothyroxine and omeprazole	Minor

58.	Propatylnitrate, acetylsalicylic acid, valsartan, hydrochlorothiazide, simvastatin, levothyroxine, metformin, quetiapine, bisoprolol, ibandronate, vitamin supplement and anastrozole	No	—	Metformin and bisoprolol; metformin and quetiapine; Quetiapine and bisoprolol; Quetiapine and valsartan	Moderate; Moderate; Moderate; Moderate
59.	Granulocyte colony growth factor, nystatin, chlorhexidine, docetaxel, trastuzumab and tamoxifen, doxorubicin	No	—	Doxorubicin and trastuzumab; Docetaxel and doxorubicin	Major; Moderate
60.	Amlodipine, atenolol, olmesartan, furosemide, anastrozole, docetaxel and doxorubicin	No	—	Amlodipine and furosemide; Atenolol and furosemide; Doxorubicin and docetaxel; Olmesartan and furosemide	Moderate; Moderate; Moderate; Moderate
61.	Metformin, glibenclamide, simvastatin, tamoxifen, doxorubicin and docetaxel	No	—	Metformin and glibenclamide; Docetaxel and doxorubicin	Moderate; Moderate
62.	Enalapril, anastrozole and doxorubicin	No	—	—	—
63.	Metformin, olanzapine, anastrozole, doxorubicin and docetaxel	No	—	Olanzapine and metformin; Doxorubicin and docetaxel	Moderate; Moderate
64.	Losartan, metformin, gabapentin, tramadol, paclitaxel, carboplatin, anastrozole, etoposide, cisplatin and hydrochlorothiazide	No	—	—	—
65.	Losartan, hydrochlorothiazide, trastuzumab, docetaxel, doxorubicin and tamoxifen	No	—	Doxorubicin and docetaxel; doxorubicin and trastuzumab	Moderate; Major
66.	Atenolol, clonazepam, anastrozole, hydrochlorothiazide, levofloxacin, doxorubicin, cyclophosphamide and fluorouracil	No	—	—	—
67.	Anastrozole, doxorubicin, cyclophosphamide,	No	—	—	—

	paclitaxel and amlodipine				
68.	Anastrozole, vitamin D, diosmin and hesperidin	No	—	—	—
69.	Anastrozole, tamoxifen, omeprazole, atenolol, furosemide, spironolactone, cilostazol, carvedilol, zoledronic acid and hydrochlorothiazide	No	—	Zoledronic acid and furosemide; Zoledronic acid and omeprazole; Tamoxifen and anastrozole	Moderate; Moderate; Moderate
70.	Tamoxifen, lansoprazole, clarithromycin, amoxicillin and polycarbophil	No	—	—	—
71.	Metoprolol, anastrozole, midazolam, ferrous sulfate and vitamin D	No	—	—	—
72.	Carvedilol, furosemide, anastrozole, clonazepam and hydrochlorothiazide	No	—	Carvedilol and furosemide	Moderate
73.	Dexamethasone, tamoxifen, omeprazole and trastuzumab	No	—	—	—
74.	Atenolol, acetylsalicylic acid, hydrochlorothiazide, omeprazole, anastrozole, zolpidem and trastuzumab	No	—	—	—
75.	Anastrozole, trastuzumab, docetaxel and doxorubicin	No	—	Docetaxel and doxorubicin; Doxorubicin and trastuzumab	Moderate; Major
76.	Omeprazole, atenolol, levothyroxine, clonazepam, fluoxetine and anastrozole	No	—	Fluoxetine and clonazepam; Levothyroxine and omeprazole; Omeprazole and fluoxetine	Minor; Minor; Minor;
77.	Anastrozole, docetaxel, doxorubicin, omeprazole, simvastatin, losartan and alprazolam	No	—	Doxorubicin and docetaxel	Moderate
78.	Losartan, hydrochlorothiazide, promethazine, anastrozole, doxorubicin, cyclophosphamide and docetaxel	No	—	Doxorubicin and docetaxel	Moderate

79.	Tamoxifen, doxorubicin and docetaxel	No	—	Doxorubicin and docetaxel	Moderate
80.	Cephalexin, anastrozole, sertraline, losartan, hydrochlorothiazide, doxorubicin and docetaxel	No	—	Sertraline and hydrochlorothiazide; Docetaxel and doxorubicin	Moderate; Moderate
81.	Tamoxifen, doxorubicin, cyclophosphamide and docetaxel	No	—	Doxorubicin and cyclophosphamide; doxorubicin and docetaxel	Major; Moderate
82.	Hydrochlorothiazide, simvastatin, glibenclamide, anastrozole, ciprofloxacin and metronidazole	No	—	—	—
83.	Tamoxifen, bromazepam, doxorubicin, cyclophosphamide and docetaxel	No	—	Doxorubicin and cyclophosphamide; doxorubicin and docetaxel	Major; Moderate
84.	Verapamil, doxorubicin, cyclophosphamide, docetaxel, gliclazide, hydrochlorothiazide and anastrozole	No	—	Doxorubicin and verapamil; Doxorubicin and docetaxel; Docetaxel and verapamil; Gliclazide and omeprazole; Gliclazide and enalapril	Major; Moderate; Moderate; Moderate; Minor
85.	Atenolol, losartan, nifedipine, anastrozole, NPH insulin and hydrochlorothiazide	No	—	Nifedipine and atenolol; NPH insulin and atenolol; NPH insulin and hydrochlorothiazide	Moderate; Moderate; Moderate
86.	Bromazepam, docetaxel, doxorubicin, trastuzumab, venlafaxine and digoxin	No	—	Digoxin and docetaxel; Digoxin and doxorubicin; Doxorubicin and trastuzumab; Doxorubicin and docetaxel	Minor; Minor; Major; Moderate
87.	Ferrous sulfate, ciprofloxacin, metronidazole, capecitabine, docetaxel, doxorubicin and zoledronic acid	No	—	Ciprofloxacin and ferrous sulfate; Capecitabine and ciprofloxacin; Doxorubicin and docetaxel	Moderate; Minor; Moderate
88.	Levothyroxine, pantoprazole, simvastatin mononitrate, etoposide and cisplatin	No	—	Levothyroxine and pantoprazole	Minor

89.	Doxorubicin, docetaxel, trastuzumab, levonorgestrel, ethinylestradiol and tamoxifen	Yes	Grade 1 taxane toxicity	Doxorubicin and docetaxel; Doxorubicin and trastuzumab	Moderate; Major
90.	Metoprolol, capecitabine, dexamethasone and losartan	No	—	—	—
91.	Docetaxel, tamoxifen, zoledronic acid, fluconazole, anastrozole, gemcitabine and cisplatin	No	—	Tamoxifen and anastrozole	Moderate
92.	Captopril, trastuzumabe, capecitabina, anastrozol, docetaxel, doxorrubicina, ciclofosfamida e pertuzumabe	No	—	Docetaxel and doxorubicin, Doxorubicin and trastuzumab	Moderate; Major
93.	Zoledronic acid, anastrozole, doxorubicin and docetaxel	No	—	Doxorubicin and docetaxel	Moderate
94.	Losartan, amitriptyline, gliclazide and doxorubicin	No	—	Doxorubicin and docetaxel	Moderate
95.	Losartan, hydrochlorothiazide, alprazolam, doxorubicin and docetaxel	No	—	Doxorubicin and docetaxel	Moderate
96.	Losartan, hydrochlorothiazide, alprazolam, doxorubicin and docetaxel	No	—	—	—
97.	Anastrozole and doxorubicin	No	—	—	—
98.	Atenolol, losartan, atorvastatin, pregabalin, zoledronic acid, anastrozole and pacitaxel	No	—	—	—
99.	Losartan, propranolol, tamoxifen, cisplatin, gemcitabine, doxorubicin and docetaxel	No	—	Docetaxel and cisplatin; Doxorubicin and docetaxel	Major; Moderate
100.	Anastrozole, rivaroxaban, enalapril, furosemide and bisoprolol	No	—	Furosemide and bisoprolol	Moderate

Source: The Authors (2024)

The non-antitumor drugs most used by patients were metformin (14 patients), furosemide (10 patients), simvastatin (16 patients), enalapril (6 patients), amitriptyline (6 patients), glibenclamide (2 patients), losartan (30 patients), atenolol (17 patients) and hydrochlorothiazide (23 patients). Potential drug interactions were also observed with these drugs, with emphasis on patients using metformin, metoprolol or furosemide, which could have caused drug interactions in, respectively, patients number 10,15, 25, 46 and 53. These interactions could cause increased blood pressure, decreased drug effect, risk of hypoglycemia or hyperglycemia in patients.

4 DISCUSSION

Among the services offered by this studied hospital are medical clinic, pediatrics, maternity ward, surgical clinic, adult and neonatal intensive care unit. Laboratory and imaging tests and specialized care in the oncology sector are also offered. Habitants of Colatina and other cities in the north and central region of the state are treated at this hospital, such as Nova Venécia, Barra de São Francisco, Jaguaré, Alto Rio Novo, Pancas, Mantenópolis, São Gabriel da Palha, Aimorés, Marilândia, Linhares and others. Oncological care began in 2013 and is considered a reference in the state. It is estimated monthly that there are around a thousand medical appointments, five hundred cycles of drug treatment, eighty surgeries and 2.5 thousand exams in the oncology sector alone.

In this study, all patients analyzed were female and the majority were aged 61 or over. In comparison with INCA data, the studied population presents general characteristics similar to the rest of Brazil, since, in the country, women are the majority population affected by breast cancer and the incidence is higher after the age of 40. (INCA, 2022)

Among the causes of drug interactions in cancer patients, we can highlight the large number of medications used at the same time, including antitumor drugs. This polytherapy in the oncology service is common, most patients use seven or more medications (Ismail *et al.*, 2020). In our work, most patients use at least five or more medications, including chemotherapy and others agents, thus increasing the chance of interaction.

Although cases of therapeutic intervention due to drug interactions are rare in the records evaluated in this article, the drug interaction investigation tools used found

many potential interactions. The main predicted interactions were doxorubucin with docetaxel or trastuzumab, docetaxel with cisplatin and interactions with non-chemotherapeutic drugs.

Anthracyclines alone can cause destruction of cardiomyocytes due to oxidative stress (Doroshow; Davies, 1986). When associated with taxanes, such as docetaxel and paclitaxel, this risk is amplified due to the increased serum concentration of anthracyclines and increased production of the cardiotoxic metabolite doxorubicinol through the action of aldehyde reductase (Salvatorelli *et al.*, 2006). It is also important to remember that taxanes alone also cause arrhythmias and sinus bradycardia (Ekholm *et al.*, 1997; Ekholm *et al.*, 2000).

Trastuzumab also generates cardiomyopathies, in this case the mechanism is due to the inhibition of survival and development pathways related to HER2, its molecular target, in cardiomyocytes (Slamon *et al.*, 2001; Crone *et al.*, 2002). When this antibody is associated with anthracyclines, there is a synergism between the cardiotoxicity mechanisms of the two drugs (Cameron *et al.*, 2019). According to information from the drug interaction investigation tools “drugs.com” and “Lexicomp® DrugInteractions”, it is necessary to prevent patients treated with trastuzumab from using anthracillins for up to 7 months in order to mitigate cardiac damage.

In another study, a high rate of drug interactions was also observed in cancer patients, 92.2% of patients presented interactions, the majority of which are non-antitumor drug-drug interactions, but interactions between drugs and chemotherapy, alternative therapies and foods were also observed. The main interaction with chemotherapy drugs led to QT prolongation, which was also found in our research. Interactions due to the use of fluconazole or ciprofloxacin were also highlighted, however, no interaction of this type was predicted in our sample (Wolf *et al.*, 2015).

In a study with 302 cancer patients, 603 drug interactions were observed using the Micromedex digital tool. Of the interactions found, 81 of them led to the intervention of a pharmaceutical professional. The most common prescriptions with risk of interaction were non-steroidal anti-inflammatory drugs, corticosteroids or coumarins (Van Leeuwen *et al.*, 2015). These drugs were rarely listed in the medical records analyzed in our study. The main consequences of the interactions found in the work of Van Leeuwen *et al* (2015) were changes in pharmacodynamics, functioning of the central nervous system, pharmacokinetics and QT interval, the latter being very common in our sample.

Since diagnosis, physical and psychological changes are triggered in cancer patients. Among the patients studied, it is possible to see a significant number of patients using antidepressants, such as amitriptyline and fluoxetine. However, interactions associated with antidepressants have been predicted. In contrast, Haque *et al* (2015) report frequent interactions between antidepressants and anti-hormonal therapy with tamoxifen, since fluoxetine, the example of the most used antidepressant in the population, tends to cause a decrease in the effect of tamoxifen.

In other Brazilian study, 161 patients of all 235 patients studied had some drug interaction, but they only identified 23 types of interactions with close monitoring necessity, and 2 types of serious interactions. The most frequent interactions were between fluorouracil and leucovorin and cyclophosphamide and doxorubicin (Monteiro et al., 2019).

Finally, it is important to highlight that cancer patients may experience cachexia and liver changes, generating pharmacokinetic changes. In this way, the risk of drug interactions is increased by the disease - regardless of the drugs used (Nishikawa *et al.*, 2021). Unfortunately, our patients' medical records, almost in their entirety, did not present data on cachexia, liver or nutritional disorders to make assessments regarding these aspects.

5 CONCLUSION

In this study, the main interactions were associated with the use of doxorubicin and docetaxel or trastuzumab. The large number of medications used by the studied patients associated with changes in the body due to cancer and advanced age increase the risk of drug interactions in these patients.

Despite the large number of expected interactions, the number of interventions was small, showing that the role of the pharmacist can be crucial in changing this scenario and improving the quality of life of cancer patients. Also, health institution should have protocols to evaluate drug interactions and avoid it. Therefore, the study highlights the importance of having a pharmaceutical professional to intervene in prescriptions and the exchange of information between professionals in the multidisciplinary team.

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