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Study of Drug Interactions in Cancer Therapy and Their Management in Cancer Patients at the Outpatient Polyclinic of General Hospital "X" in 2020

Anak Agung Ngurah Putra Riana Prasetya[1]*, Mahadri Dhrik[2], Pande Made Desy Ratnasari[1], Ni Luh Sri Adi Suryani[1]

[1] Bachelor of Pharmacy Study Program, Sekolah Tinggi Farmasi Mahaganesha, Denpasar, Bali, Indonesia
[2] Diploma of Pharmacy Study Program, Sekolah Tinggi Farmasi Mahaganesha, Denpasar, Bali, Indonesia

ABSTRACT: Chemotherapy is commonly used in cancer patients either as a monotherapy or in combination, as it demonstrates higher effectiveness and lower toxicity compared to single-agent use, while also preventing drug resistance. The combination of chemotherapy drugs, or their use alongside supportive drugs, can increase the risk of drug interactions that may affect treatment outcomes. The purpose of this research is to examine and offer suggestions for the management of medication interactions in cancer patients at the X Cancer Centre polyclinic of X Denpasar Hospital in 2020. The present investigation is a cross-sectional descriptive study with retrospective data collection from medical records in 2020. Drug interaction data were analyzed using Drugs.com, Lexicomp, and Stockley to assess the type of interaction, risk level, severity, and management of each interaction. The results indicated that the most common types of cancer were breast cancer (62.7%) and lymphoma (10.2%), with combination chemotherapy being used in 73.97% of cases. The most frequent type of interaction was pharmacodynamic interaction (50.42%), with risk level C (35.53%) and moderate severity (69.07%). The most common interactions were between chemotherapy drugs and supportive drugs (46.47%). The recommended management of potential drug interactions in cancer patients includes providing a time gap between drug administrations.

Keywords: Drug interactions; cancer; chemotherapy

*Corresponding author:
Name : Anak Agung Ngurah Putra Riana Prasetya
Email : gungtra.apoteker95@gmail.com
Address : Sekolah Tinggi Farmasi Mahaganesha, Denpasar, Bali, Indonesia

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INTRODUCTION

Cancer is a condition involving the abnormal growth of body cells that can develop and spread to other parts of the body, disrupting organ growth and potentially leading to death (Yeoh et al., 2015). Cancer patients in the world are estimated to reach 19.3 million cases, with 10 million deaths, and as many as 68 thousand cases of breast cancer are found in Indonesia, with 22 thousand deaths. Common cancer cases in Indonesia are lung cancer, breast cancer, prostate cancer, colorectal cancer, stomach cancer, and liver cancer (Firdaus & Susilowati, 2023; Sung et al., 2021). The growth and development of cancer cells are influenced by the disruptions in deoxyribonucleic acid (DNA) formation, which triggers abnormalities in gene division (gene mutation). Several factors contribute to cancer cell growth, including exposure to carcinogenic substances, oncogenic viruses, environmental factors, economic factors, diet, and alcohol consumption (Alipour, 2021; Sun et al., 2020).

Chemotherapy is one of the commonly used methods as an anticancer agent, used singly or in combination, with a mechanism of action that suppresses proliferation, spread and destroys cancer cells (cytotoxic). The cytotoxic effect of chemotherapy drugs destroys cancer cells and affects normal cells, which can lead to harmful side effects (Firdaus & Susilowati, 2023). Combinations of chemotherapy drugs are commonly used because they are more effective and have lower toxicity compared to single-agent use, and they can prevent or slow drug resistance (Rusdi et al., 2023). Another widely used treatment approach is the combination of chemotherapy drugs with supportive drugs, which are used as premedication before chemotherapy and as post-chemotherapy therapy.

The use of drug combinations can cause drug-related problems (DRP). Drug-related problems (DRP) are unexpected events caused by treatment that can potentially affect and disrupt the success of therapy. One of the issues within DRPs is drug interactions, which can affect clinical outcomes during treatment (Mantang et al., 2023). Drug interactions are categorised into three types, namely pharmaceutical interactions, pharmacokinetic interactions, and pharmacodynamic interactions. Drug interactions may occur due to excessive drug use in a single prescription, known as polypharmacy. Another study reported that the incidence of DRP due to ineffective medication was 26.67%, and due to drug interactions was 66.67% (Nayak et al., 2021).

Based on this, several studies on drug interactions in cancer patients have been conducted. One study found that the potential for drug interactions in cancer patients at X West Java hospital from 2019 to 2021 involved 428 cases, with 88.17% having moderate significance (Rusdi et al., 2023). Another study mentioned that prescribing more than seven types of drugs, or three or more types of cancer drugs, carries a high risk of drug interactions (Ismail et al., 2020). Another study examining drug interactions in cancer patients found that 50.1% of drug interactions were caused by pharmacodynamic mechanisms, 27% by pharmacokinetic mechanisms, and 23.6% had an unknown interaction mechanism (Ramasubbu et al., 2021).

Based on these studies, the high potential for drug interactions during treatment can affect treatment outcomes and increase the risk of side effects. Drug interactions can be mitigated by assessing the interactions of the drugs given to cancer patients (Faizah, 2018). Thus, the purpose of this study was to evaluate the possibility of drug interactions and offer suggestions for handling drug interaction incidents in cancer patients at the X General Hospital Denpasar's X Cancer Centre outpatient clinic over the course of 2020.

METHODS

Research Design

This study used an observational cross-sectional design and employed descriptive methods with retrospective data collection from the outpatient polyclinic at X Cancer Center, X Denpasar General Hospital. The study population and sample included all medical records and pharmacy data of patients diagnosed with cancer who underwent chemotherapy in 2020.

Sampling Technique

The sampling technique in this study uses purposive sampling with specific considerations in sampling. The inclusion criteria in the study were cancer patients undergoing outpatient chemotherapy who had complete drug data (chemotherapy regimen, premedication drugs, and post-chemotherapy). The exclusion criteria were patients undergoing chemotherapy whose medical records had unclear or unreadable drug names, and cancer patients undergoing chemotherapy did not receive premedication therapy or post-chemotherapy drugs. Based on the inclusion and exclusion criteria, a total of 118 samples were obtained.

Research Instruments

The research instrument used was a data collection table containing the patient's name initials, medical record number, gender, chemotherapy drugs used, premedication drugs, and post-chemotherapy drugs, which would later be placed in the drug interaction assessment analysis table. The data obtained was stored using the Microsoft Excel application. The type of data used was quantitative data, which included patient population data, chemotherapy drugs used, and drugs used before and after undergoing chemotherapy.

Data Analysis

Demographic and drug interaction data were analyzed descriptively using a percentage table. Analysis of patient demographics included data on gender, age, occupation, and type of cancer experienced by the patient, while the drug interactions analysis was determined based on the significance standards found on the official website of Lexicomp (2023), Drugs.com (2023), and Stocktey's Drug Interactions (2015). Drug interaction analysis was conducted by comparing interactions that occurred in patients with those recorded in the literature. The percentage of drug interactions was determined based on the types of drug interactions that occurred, the level of risk factors set by the Food and Drug Administration (FDA), and the significance of interactions from several risk factors reviewed based on the severity caused by drug interactions (severity). The following equation was used in calculating the percentage of drug interaction events and the significance of interactions is as follows:

%Potential drug interactions = $\frac{Number\ of\ drug\ interaction\ types}{Total\ of\ drug\ interactions}\ x\ 100\%$

%Potential drug interactions based on significance=

$$\frac{Number\ of\ interactions\ by\ significance\ category}{Total\ of\ drug\ interactions\ by\ significance\ category}\ x\ 100\%$$

Analysis of drug interactions based on the level of risk is grouped into several categories: category A indicates that there is no evidence of drug interactions, category B indicates evidence of potential drug interactions with little clinical effect, category C

indicates clinical significance so that monitoring is required, Category D indicates the need for changes (dose, alternative therapy, or monitoring) and Category X indicates that avoiding it is advisable due to its high risk. Meanwhile, severity-based analysis classified interactions as major (potentially causing death or permanent disability), moderate (resulting in clinical status changes), or minor (with negligible effects that do not require additional therapy) (Shetty et al., 2018; Yuliawati et al., 2021). This study also included management recommendations for each identified drug interaction as supporting data.

RESULT AND DISCUSSION

Characteristics Sample

A total of 118 samples met the inclusion criteria of cancer patients undergoing outpatient chemotherapy at the X Cancer Center Polyclinic, X Denpasar General Hospital, in 2020. Table 1 shows that the highest average age of cancer patients falls within the 44 to 53 year range (32%), with a higher proportion of female patients (82%) compared to male patients (18%). Females are at greater risk of developing cancer due to hormonal influences, such as estrogen, which plays a role in regulating menstruation and the menopausal process. Prolonged exposure to this hormone can increase cancer risk (Hasnita & Arif Harahap, 2019; Wardana & Ernawati, 2019). Twelve types of cancer were identified among the patients, with the most common being breast cancer (62.7%), non-Hodgkin lymphoma (10.2%), rectal cancer (7.6%), and colorectal cancer (5.9%). Previous studies have shown that most breast cancer cases occur between the ages of 45 and 64, due to the increased cancer risk associated with aging and accumulated genetic damage (Elmika & Adi, 2020; Sari & Gumayesty, 2016).

Drug Utilization Profile

Chemotherapy drugs are cytostatic agents used to inhibit the proliferation of cancer cells and induce cell destruction. These drugs, whether used as monotherapy or in combination, are commonly administered to cancer patients (Firdaus & Susilowati, 2023). At X General Hospital, chemotherapy regimens include both monotherapy and combination therapy. This study found that 26.03% of patients received chemotherapy as monotherapy, while 73.97% were treated with combinations of two or more chemotherapy drugs.

Based on the data in Table 2, the most frequently used combination of two chemotherapy drugs was carboplatin and paclitaxel, accounting for 7.32%. This combination is commonly used in patients with triple-negative breast cancer (TNBC), an aggressive form of breast cancer that does not respond to standard therapies. TNBC lacks the expression of several receptors, such as progesterone and estrogen receptors, but often involves overexpression of the Human Epidermal Growth Factor Receptor 2 (HER-2), a receptor that regulates cell growth and repair in breast tissue (Amtiria et al., 2018; Permana et al., 2019; Yu et al., 2020).

This study also identified combinations involving three chemotherapy drugs, with the most common being 5-Fluorouracil, Doxorubicin, and Cyclophosphamide, used in 13.82% of cases. This regimen significantly reduces the risk of breast cancer recurrence by interfering with DNA replication during the cancer cell development cycle. It is typically administered intravenously every three weeks for six cycles (Irawati & Sardjan, 2022; Pereira-Oliveira et al., 2019). The use of combination chemotherapy aims to improve

tolerability and effectiveness while reducing drug resistance in cancer patients (Wu et al., 2020).

Table 1. Patients Demographics

Patient Demographics		**Total**	**%**
age	24 – 33	6	5
	34 – 43	25	21
	44 – 53	38	32
	54 - 63	34	29
	64 - 73	15	13
Total		118	100
Sex	Female	97	82
	Male	21	18
Total		118	100
Type Cancer	Breast Cancer	74	62.7
	Non-Hodgkin's Lymphoma	12	10.2
	Rectal Cancer	9	7.6
	Colon Cancer	7	5.9
	Cervical Cancer	4	3.4
	Ovariun Cancer	3	2.5
	Plasma Cell Cancer	3	2.5
	Nasopharyngeal Cancer	2	1.7
	Blood Cancer	1	0.8
	Esophageal Cancer	1	0.8
	Lung Cancer	1	0.8
	Prostat Cancere	1	0.8
Total		118	100

Table 2. Chemotherapy Drugs Used

Drug	**Total**	**%**
Monotherapy		
Trastuzumab	7	5.69%
Gemcitabine	5	4.09%
Paclitaxel	4	3.25%
Capecitabine	4	3.25%
Bevacizumab	3	2.44%
Other	9	7.31%
Total		26.03%
2 Combination Therapy		
Carboplatin + Paclitaxel	9	7.32%
Doxorubicin + Paclitaxel	9	7.32%
Capecitabine + Oxalipatin	8	6.50%
Cyclophosphamide + Doxorubicin	5	4.07%
Paclitaxel + Trastuzumab	3	2.44%
Pertuzumab + Trastuzumab	3	2.44%
Other	15	12.19%

Drug	Total	%
3 Combination Therapy		
5-Fluorouracil + Doxorubicin + Cyclophosphamide	17	13.82%
Doxorubicin + Cyclophosphamide + Vincristine	11	8.94%
5-Fluorouracil + Irinotecan + Leucovorin	3	2.44%
Doxorubicin + Paclitaxel + Trastuzumab	2	1.63%
Other	5	4.05%
4 Combination Therapy		
5-Fluorouracil + Bevacizumab + Leucovorin + Oxaliplatin	1	0.81%
Total		**73.97%**
Total Monotherapy + Combination Therapy		**100%**

In addition to chemotherapy drugs, cancer patients commonly use supportive medications (Table 3) to reduce or manage the side effects caused by chemotherapy. These supportive therapies include drugs administered before (premedication) and after (post-medication) chemotherapy. The most frequently used supportive drugs were antihistamines (31.61%), corticosteroids (31.31%), and 5-HT3 receptor antagonists (21.88%). First-generation antihistamines are commonly used in cancer patients undergoing chemotherapy to manage hypersensitivity reactions and side effects associated with chemotherapy drugs (Fritz et al., 2021). Other studies have also reported that the use of antihistamines (e.g., diphenhydramine), corticosteroids (e.g., dexamethasone), and 5-HT3 receptor antagonists (e.g., ondansetron) effectively reduces and controls chemotherapy-induced nausea and vomiting (Shinta R & Surarso, 2016).

Table 3. The usage of other drugs

Drug	Total	%
Antihistamine	104	31,61%
Corticosteroids	103	31,31%
5-HT3 Receptor Antagonists	72	21,88%
Supplement	26	7,90%
Proton Pump Inhibitor (PPI)	9	2,74%
Analgesics	6	1,82%
Anticoagulan	1	0,30%
H2 Antagonist	1	0,30%
Other	7	2,13%
Total	329	100%

Drug Interaction Assessment

The use of chemotherapy drugs in combination with supportive therapy in cancer patients carries a high risk of drug interactions. This potential arises from the concurrent use of multiple medications, often due to comorbidities and the advanced age of patients (Rabba et al., 2020; Riechelmann & Krzyzanowska, 2019). Studying drug interactions is essential for estimating potential risks and planning appropriate management strategies to reduce or prevent adverse interactions (Hammad et al., 2017).

This study reviewed drug interactions in cancer patients undergoing chemotherapy using both free and paid resources, such as Drugs.com, Lexicomp, and Stockley's Drug Interactions. The results indicated that the most common type of interaction was

pharmacodynamic (50.42%). Similar findings were reported in another study, where pharmacodynamic interactions accounted for 50.1%, surpassing pharmacokinetic (26.6%) and unknown (23.3%) interactions (Ramasubbu et al., 2021). One example of a pharmacodynamic interaction identified in this study was between doxorubicin and 5-fluorouracil, which can lead to myelosuppression and gastrointestinal bleeding (Nayak et al., 2021).

Pharmacodynamic interactions occur when two drugs share similar or opposing pharmacological targets, therapeutic effects, or side effects. These interactions typically involve active compounds that mutually alter pharmacological effects, either reinforcing, adding to, or antagonizing each other, leading to unwanted reactions (Ramdani et al., 2022). Another type of potential interaction observed was pharmacokinetic, accounting for 27.97%. An example of this interaction is between doxorubicin and dexamethasone, where dexamethasone may decrease the blood levels of doxorubicin (Drug.com, 2023). Pharmacokinetic interactions occur when one drug affects the absorption, distribution, metabolism, or excretion of another drug, altering plasma concentrations. This effect can result from the inhibition or induction of cytochrome P450 (CYP) enzymes in the body (Rizo et al., 2020).

The assessment of drug interactions based on risk level is categorized into five groups: A, B, C, D, and X. As shown in Table 4, the most common risk levels were C (35.53%) and D (34.21%). Based on severity, drug interactions can be classified as major, moderate, or minor. Major interactions have significant clinical consequences, moderate interactions can alter the patient's clinical status, and minor interactions cause mild disturbances that do not substantially affect therapeutic outcomes (Feinstein et al., 2015). The most frequent interaction severity in this study was moderate (69.07%).

Table 4. Potential Interaction Characteristics

Characteristic		**%**
Type Interactions	Pharmacodynamic	50.42%
	Pharmacokinetic	27.97%
	Unknown	21.61%
Total		**100%**
Risk Level	C	35.53%
	D	34.21%
	B	30.26%
Total		**100%**
Severity	Moderate	69.07%
	Mayor	19.49%
	Minor	11.44%
Total		**100%**

Table 5 shows that the potential for drug interactions is higher in the combination of chemotherapy drugs and supportive drugs (46.47%) than in the interaction between chemotherapy drugs alone (41.08%) or between supportive drugs alone (12.45%). Similar findings have been reported in other studies, which also indicated that the potential for drug interactions was higher when chemotherapy drugs were combined with supportive drugs (Laban et al., 2021). The combination of dexamethasone and paclitaxel (25%) was the most frequently observed drug interaction in cancer patients, followed by the

combination of cyclophosphamide and ondansetron (18.75%), and the interaction between doxorubicin and dexamethasone (11.61%). The interaction between dexamethasone and paclitaxel is a pharmacokinetic interaction with moderate severity. Dexamethasone is an inducer of the cytochrome P450 enzyme CYP3A4, which can lower paclitaxel levels in the blood, thus reducing its effectiveness. Management strategies include monitoring the therapeutic response to paclitaxel, administering dexamethasone 30 minutes prior to paclitaxel infusion, and using dexamethasone as premedication to reduce the risk of hypersensitivity reactions caused by paclitaxel (D'Errico et al., 2020).

We classify the interaction between cyclophosphamide and ondansetron as an unknown interaction of minor severity, with a risk level of B. Ondansetron may reduce the pharmacological effects and alter the systemic exposure of cyclophosphamide. Both drugs are metabolised in the liver, with ondansetron having an onset time of 30 minutes and cyclophosphamide having a half-life of 3–12 hours, excreted through urine. Management strategies for this combination include allowing a 1–2 hour gap between administrations or considering safer antiemetic options, such as palonosetron (Drug.com, 2023; Koni et al., 2022; Ramasubbu et al., 2021).

The potential interaction between oxaliplatin and ondansetron is classified as moderate in severity, with a pharmacodynamic interaction type that has an additive effect, increasing the risk of irregular heart rhythms, which could potentially lead to death (Drug.com, 2023; Williamson & Polwart, 2016). Management strategies include closely monitoring the QT interval via electrocardiogram (ECG). Patients should be advised to seek immediate medical attention if they experience dizziness or irregular heartbeats. To minimize the risk of interaction, the ondansetron dose can be adjusted to 8 mg, or alternatives such as granisetron or palonosetron, other drugs in the 5-HT3 receptor antagonist class, can be considered (de Lemos et al., 2019; Drug.com, 2023).

Based on Table 5, 41.08% of potential drug interactions were observed in combinations of chemotherapy drugs. The most common interaction was between paclitaxel and trastuzumab (15.78%), which involves an unknown interaction type with moderate severity. This combination is frequently used as a first-line treatment in patients with metastatic breast cancer. It may increase the serum concentration of trastuzumab while decreasing the serum concentration of paclitaxel, which can increase the risk of cardiotoxicity with long-term use of trastuzumab (Büyükköroğlu et al., 2016). Management strategies for this interaction include periodic monitoring of the patient's heart function via ECG. Patients should also be advised to consult their doctor immediately if they experience symptoms such as chest pain, nausea, sweating, coughing, or wheezing (Drug.com, 2023).

Another significant interaction was observed between doxorubicin and cyclophosphamide, which is classified as a pharmacokinetic interaction with major severity and risk level C. This interaction increases the risk of doxorubicin-induced cardiotoxicity, which can lead to permanent heart damage or even death (Jamali et al., 2021; Kurniawati et al., 2021). To manage this interaction, it is recommended to monitor heart function before and during treatment, consider using a lower dose of cyclophosphamide compared to doxorubicin, administer cyclophosphamide via infusion, and use liposomal doxorubicin to reduce toxic effects (Atalay et al., 2014; Drug.com, 2023).

Table 5. Category of Potential Drug Interactions

NO	Drug	Other Drug	Potentially Interaction			Total	%
			Severity Level	Risk Level	Type Interaction		
Potential Chemotherapy Drug Interactions with Ancillary Drugs (46.47%)							
1	Dexamethasone	Paclitaxel	Moderat*	-	PK	28	25%
2	Cyclophosphamide	Ondansetron	Minor**	B	Unknown	21	18.75%
3	Doxorubicin	Dexamethasone	Moderat*	-	PK	13	11.61%
4	Dexamethasone	Vincristine	Moderat*	-	PK	12	10.71%
5	Oxaliplatin	Ondansetron	Moderat*	-	PD	10	8.93%
6	Doxorubicin	Ondansetron	Moderat*	-	PD	8	7.14%
7	Carboplatin	Pantoprazole	Moderat*	-	PD	7	6.25%
8	Doxorubicin	Palonosetron	Moderat*	-	PD	6	5.36%
9	Dexamethasone	Irinotecan	Moderat*	-	PK	3	2.68%
10	Dexamethasone	Bortezomib	Minor **	B	PK	2	1.79%
11	Dexamethasone	Vinorelbine	Moderat*	-	PK	1	0.89%
12	Capecitabine	Omeprazole	Moderat**	C	Unknown	1	0.89%
Total							100%
Potential Interactions Between Chemotherapy Drugs (41.08%)							
1	Paclitaxel	Trastuzumab	Moderat*	-	Unknow	15	15.78%
2	Cyclophosphamide	Doxorubicin	Mayor**	C	PK	13	13.68%
3	Doxorubicin	5-Fluorouracil	Moderat*	-	PD	13	13.68%
4	Cyclophosphamide	5-Fluorouracil	Moderat*	-	PD	13	13.68%
5	Doxorubicin	Paclitaxel	Mayor**	D	PK	11	11.57%
6	Carboplatin	Paclitaxel	Mayor**	D	Unknown	9	9.47%
7	Oxaliplatin	Capecitabine	Moderat*	-	PD	6	6.31%
8	Leucovorin	5-Fluorouracil	Mayor*	-	PD	5	5.26%
9	Doxorubicin	Trastuzumab	Mayor*	-	Unknown	3	3.15%
10	Carboplatin	Gemcitabine	Moderat*	-	Unknown	2	2.10%
11	Oxaliplatin	5-Fluorouracil	Moderat*	-	PD	2	2.10%
12	Tamoxifen	Goserelin	Moderat*	-	PK	2	2.10%
13	Doxorubicin	Carboplatin	Moderat**	D	PD	1	1.05%
Total							100%
Potential Interactions Between Ancillary Drugs (12.45%)							
1	Ondansetron	Palonosetron	Moderat*	-	PD	10	33.33%
2	Dexamethasone	Alprazolam	Minor*	-	PD	4	13.13%
3	Dexamethasone	Celecoxib	Moderat*	-	PD	3	10.10%
4	Dexamethasone	Oxycodon	Mayor*	-	PD	2	6.67%
5	Diphenhydramine	Oxycodon	Mayor**	D	PD	2	6.67%
6	Ondansetron	Oxycodon	Moderat*	-	PD	1	3.33%
7	Dexamethasone	Rivaroxaban	Moderat*	-	PK	1	3.33%
8	Dexamethasone	Meloxicam	Moderat**	C	PD	1	3.33%
9	Diphenhydramine	Alprazolam	Moderat**	C	PD	1	3.33%
10	Diphenhydramine	Metoclorpramide	Moderat**	C	PD	1	3.33%
11	Diphenhydramine	Atropine sulfate	Moderat**	C	PD	1	3.33%
12	Diphenhydramine	Amitriptyline	Moderat**	C	PD	1	3.33%
13	Amitriptyline	Morfine	Mayor**	D	PD	1	3.33%
14	Cimetidine	Alprazolam	Moderat**	C	PK	1	3.33%
Total							100%

*drug.com; **Lexicomp; PK= Pharmacokinetics; PD= Pharmacodynamics (Drug.com. 2023; Lexicom. 2023)

A potential interaction was also found between supporting drugs, specifically ondansetron and palonosetron, which accounted for 33.33% of interactions in this category. This interaction is classified as pharmacodynamic with moderate severity. The

combined use of these drugs can increase the risk of QT prolongation, which may lead to arrhythmias and death (Novita & Destiani, 2019). Management strategies include monitoring heart rhythm using ECG and ensuring that there is a time interval between the administration of ondansetron and palonosetron. If possible, palonosetron alone should be used, as it is a second-generation 5-HT3 receptor antagonist with stronger receptor affinity, a longer elimination half-life (approximately 40 hours), and is more effective in controlling nausea and vomiting during chemotherapy (Drug.com, 2023; Umar, 2018).

Table 6. Drug Interaction Management

No	Drug	Other Drug	Interactions based on literature	Restriction Management based on literature
Potential Chemotherapy Drug Interactions with Ancillary Drugs (46,47%)				
1	Dexamethasone	Paclitaxel	Co-administration with drugs that induce CYP450 2C8 and/or 3A4 (dexamethasone) may reduce plasma concentrations or blood levels of Paclitaxel*.	• Monitoring for decreased therapeutic response to paclitaxel* • Dexamethasone administered no later than 30 minutes before paclitaxel
2	Cyclophosphamide	Ondansetron	Ondansetron may decrease the serum concentration of Cyclophosphamide**.	• No intervention required*
3	Doxorubicin	Dexamethasone	Co-administration with drugs that induce CYP450 2C8 and/or 3A4 (dexamethasone) may reduce plasma concentrations or blood levels of Doxorubicin*.	• Monitoring for decreased therapeutic response to Doxorubicin* • Dexamethasone administered no later than 1-2 hours before Doxorubicin
4	Dexamethasone	Vincristine	Decreases the effect of plasma concentrations of Vincristine*	• Dexamethasone is administered 1-2 hours before vincristine*
5	Oxaliplatin	Ondansetron	Increased risk of QT prolongation*	• Regular monitoring of cardiac function and rhythm by performing an electrocardiogram* • Dose adjustment is required, and alternatives such as Granisetron or palonosetron may be substituted if possible
6	Doxorubicin	Ondansetron	Increased risk of QT prolongation*	• Regular monitoring of heart function and rhythm*
7	Carboplatin	Pantoprazole	Use of proton pump inhibitors (pantoprazole) may increase hypomagnesia*	• Clinical and laboratory monitoring of hematologic and non-hematologic toxicity is required* • Substitution with histamine type-2 receptor antagonists or the addition of sucralfate is recommended if hypomagnesia is indicated.
8	Doxorubicin	Palonosetron	Increased risk of QT prolongation*	• Regular monitoring of heart function and rhythm*

No	Drug	Other Drug	Interactions based on literature	Restriction Management based on literature
9	Dexamethasone	Irinotecan	Reduced therapeutic effect and blood levels of irinotecan*	• Monitoring the pharmacological response of irinotecan* • Dexamethasone is given 30 minutes before irinotecan
10	Dexamethasone	Bortezomib	Decreases serum concentration of bortezomib**	• No intervention required*
11	Dexamethasone	Vinorelbine	Reduces the effects and blood levels of vinorelbine*	• Special care is needed if we use the medicine together* A change of medication is recommended if possible*
12	Capecitabine	Omeprazole	Use of proton pump inhibitors (omeprazole) may reduce the therapeutic effect of capecitabine**	• Special monitoring of reduced efficacy of capecitabine is required** • Consideration of the use of simethicone
Potential Interactions Between Chemotherapy Drugs (41,08%)				
1	Paclitaxel	Trastuzumab	Paclitaxel may enhance the cardiotoxic effects of trastuzumab	• Regular monitoring of the patient's heart function by conducting an electrocardiogram* • Recommended that if the patient experiences symptoms of chest pain, immediately consult a doctor.*
2	Cyclophosphamide	Doxorubicin	Cyclophosphamide increases the cardiotoxic effects of doxorubicin	• Monitor heart function** • Suggested a lower dose of cyclophosphamide than doxorubicin** • Suggested use of liposomal doxorubicin to reduce cardiotoxic risk**
3	Doxorubicin	5-Fluorouracil	Concurrent or sequential administration may cause additive toxicity, especially in the bone marrow and gastrointestinal tract.*	• Clinical monitoring as well as laboratory examination of haematologic and non-haematologic toxicity and dose adjustment of each drug*
4	Cyclophosphamide	5-Fluorouracil	Increased risk of side effects, especially those affecting the bone marrow and gastrointestinal tract*	• Monitoring side effects with clinical and laboratory monitoring for hematologic and non-hematologic toxicity* • Dose adjustment is required if the patient develops fever, chills, and diarrhea during treatment.*
5	Doxorubicin	Paclitaxel	Paclitaxel may increase doxorubicin-induced cardiovascular toxicity.**	• Monitoring of heart function** • Doxorubicin is given first, at least 24 hours before paclitaxel, and it is recommended to add the cytoprotective drug dexrazoxane.

No	Drug	Other Drug	Interactions based on literature	Restriction Management based on literature
6	Carboplatin	Paclitaxel	Increased risk of myelosuppressive side effects from Paclitaxel **	• Paclitaxel infusion is given first before carboplatin; this order of administration reduces platelet toxicity** • If the patient develops peripheral neuropathy, this combination should be stopped immediately to reduce further damage
7	Oxaliplatin	Capecitabine	Causes additive toxicity, especially in the bone marrow and gastrointestinal tract*	If co-administered, more frequent monitoring of doses tailored to the patient's needs is required*
8	Leucovorin	5-Fluorouracil	The combination of these drugs has a synergistic effect, potentially causing cardiotoxicity, cardiomyopathy, heart failure, diarrhoea, mucositis, and myelosuppression.	• Special monitoring of the dose, it is recommended that the dose of 5-FU is smaller than leucovorin, and the potential toxicity of 5-FU, such as thrombocytopenia, neutropenia, can be monitored by conducting laboratory tests * • The use of this drug combination should not be used or continued if the patient has symptoms of gastrointestinal toxicity until the symptoms disappear*
9	Doxorubicin	Trastuzumab	Trastuzumab induced doxorubicin, resulting in increased cardiotoxic effects such as cardiomyopathy*	• Monitoring of blood drug levels and heart function* • If possible, the use of anthracycline therapy should be avoided for up to 7 months after discontinuation of trastuzumab*
10	Carboplatin	Gemcitabine	Increased risk of side effects, neurotoxicity, nephrotoxicity, and ototoxicity*	• Use of Carboplatin infusion after gemcitabine* • During the administration of this combination, do not use simultaneously with NSAID drugs
11	Oxaliplatin	5-Fluorouracil	Increased neutropenia and anemia incidence, peripheral neuropathy, and hypersensitivity reactions	• Clinical and laboratory monitoring of hematologic and non-hematologic toxicities* • Calcium channel blocker (CCB) drugs such as amlodipine are recommended to reduce the risk of oxaliplatin-induced peripheral neuropathy
12	Tamoxifen	Goserelin	Increased risk of irregular heart rhythms with potential death, and electrolyte disturbances*	Recommended patients have their electrolytes and heart function checked by performing an ECG*

No	Drug	Other Drug	Interactions based on literature	Restriction Management based on literature
13	Doxorubicin	Carboplatin	Increases the risk of additive toxicity effects, especially in the bone marrow and gastrointestinal tract**	• Clinical monitoring and laboratory examination of hematological, non-hematological toxicity, and dose adjustment of each drug ** • Monitoring of side effects such as nausea and vomiting **
Potential Interactions Between Ancillary Drugs (12,45%)				
1	Ondansetron	Palonosetron	Increased cardiac rhythm*	• Closely monitoring the patient's heart rhythm by performing an ECG * • Given a time lag in its use, for example, palonosetron is given as premedication while ondansetron is given as post-chemotherapy, or if possible, use palonosetron alone
2	Dexamethasone	Alprazolam	Co-administration with drugs that induce CYP450 2C8 and/or 3A4 (dexamethasone) may reduce plasma concentrations or blood levels of Alprazolam*.	Recommended to allow about 1-2 hours between dexamethasone and alprazolam*
3	Dexamethasone	Celecoxib	Increased effects of gastrointestinal ulceration and bleeding*	Monitoring risk of side effects*
4	Dexamethasone	Oxycodon	Co-administration with drugs that induce CYP450 2C8 and/or 3A4 (dexamethasone) may reduce plasma concentrations or blood levels of Oxycodon *.	• Monitoring pharmacologic responses* • If used concomitantly, limit the dose of the drug to the minimum or as needed to achieve the desired therapeutic effect*
5	Diphenhydramine	Oxycodon	increased depressant effects on the central nervous system**	• Monitoring depression of respiration, central nervous system** • If used concomitantly, dose adjustment and dose titration are required, especially at treatment initiation**
6	Ondansetron	Oxycodon	Increased risk of serotonin syndrome*	Special monitoring for serotonin syndrome symptoms during treatment*
7	Dexamethasone	Rivaroxaban	Dexamethasone may reduce blood levels of rivaroxaban*	Dose adjustment and time interval for administration are recommended*
8	Dexamethasone	Meloxicam	Increased effects of gastrointestinal ulceration and bleeding*	• Monitoring side effects ** • Recommended during the use of meloxicam to add drugs that can help protect the intestines and stomach**

No	Drug	Other Drug	Interactions based on literature	Restriction Management based on literature
9	Diphenhydramine	Alprazolam	Increased risk to the central nervous system due to sedative effects**	• If used together, dose adjustment and dose titration are required, especially at treatment initiation** • Second-generation antihistamines that do not increase sedative effects are recommended**
10	Diphenhydramine	Metoclorpramide	Increased diastonic ripple and depressant effects on the central nervous system**	Monitoring depression of respiration, central nervous system**
11	Diphenhydramine	Atropine sulfate	Increased additive toxic effect of one of the drugs**	Monitoring depression of respiration, central nervous system**
12	Diphenhydramine	Amitriptyline	Increased additive toxic effect of one of the drugs**	Monitoring depression of respiration, central nervous system**
13	Amitriptyline	Morfine	Increased risk of serotonin syndrome**	• Monitoring for depression of respiration, central nervous system** • Limit the dose and duration of both drugs, and the initiation of opioid dose reduction should be considered
14	Cimetidine	Alprazolam	Cimetidine may prolong the effects of alprazolam**	If used, consider reducing the alprazolam dose by one-third or dosing to twice daily

*drug.com **Lexicomp (Drug.com, 2023; Lexicom, 2023)

The use of chemotherapy and supportive drugs in cancer patients presents a high potential for drug interactions. Special attention and monitoring are essential to prevent Drug-Related Problems (DRPs). Studying potential drug interactions in cancer patients can improve the quality of healthcare services, enhance therapeutic outcomes, and ultimately increase the quality of life for patients while minimizing the risk of drug interactions. This proactive approach ensures that drug efficacy is optimized and patient safety is maintained.

CONCLUSION

The results of this study indicate that chemotherapy drug combinations are more commonly used in cancer patients, alongside additional supportive therapies, such as antihistamines, corticosteroids, and 5-HT3 receptor antagonists, which are employed as premedication and post-chemotherapy treatments. The most frequently encountered drug interactions were pharmacodynamic interactions (50.42%), major severity interactions (69.07%), and risk level C interactions (35.53%) at the X Cancer Center Polyclinic of RSU X Denpasar. Recommended management strategies to address these potential drug interactions include adjusting the timing of drug administration, considering alternative drug combinations, and ensuring ongoing monitoring of drug interactions by pharmacists or other healthcare professionals.

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AUTHOR CONTRIBUTION

AANPRP: Concepts or ideas; design; definition of intellectual content; literature search; experimental studies; data analysis; manuscript preparation.
MD: literature search; experimental studies; data analysis.
PMDR: Manuscript editing; manuscript review.
NSLAS: Definition of intellectual content; literature search, manuscript preparation.

ETHICS APPROVAL

Ethical approval for this study was granted by the Health Research Ethics Committee of Stikes Bina Usada Bali under ethical number 107/EA/KEPK-BUB-2024.

CONFLICT OF INTEREST

None to declare

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