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Scientific Analysis with a Retrospective Method on the Incidence and Severity of Adverse Drug Reactions in Hospitalized Cancer Patients

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Abstract: Adverse Drug Reactions (ADRs) often result from omissions or inadequate use of preventative measures, making them definitely or probably preventable. Discrepancies between clinical severity and patients' perceptions of ADRs' impact on their well-being highlight the need for targeted interventions. This study focused on the frequency, manifestations, and severity of ADRs from chemotherapeutic agents, utilizing a cross-sectional design with data from ADR reports spanning November 2021 to October 2023 at dr. Saiful Anwar General Hospital, Indonesia. A total of 177 ADRs were analyzed descriptively. Of these, 99 (55.93%) occurred in women, with the highest incidence in the 19–60-year age group (77.40%). The most common malignancies were Chronic Myeloid Leukemia (10.17%), Colorectal Malignancy, and Non-Hodgkin Lymphoma (9.60% each). ADRs related to chemotherapy constituted 41.80%, involving drugs such as cisplatin, oxaliplatin, afatinib, imatinib, and Doxorubicin. The severity distribution was 70.37% mild, 27.16% moderate, and 2.47% severe. Monitoring and reporting these ADRs are crucial for patient safety and preventing recurrence.

Keywords: ADRs; Adverse drug reaction; Antineoplastic drugs; Cancer; Pharmacovigilance

Introduction

Cancer is one of the diseases with a significant impact on global health and is the 6th leading cause of death worldwide (WHO, 2024). Cancer therapy often uses a multimodal approach with various mechanisms of action, such as chemotherapy, radiotherapy, immunotherapy, hormonal therapy, surgery, biological agents, and cryosurgery. Although the use of these drugs has provided great benefits in improving the survival rate and quality of life for cancer patients, antineoplastic agents, which have a narrow therapeutic index, are more cytotoxic and can damage normally dividing cells as well as cancer cells. Therefore, they are often associated with unwanted incidents or side effects that can affect patient tolerability and adherence to treatment (Sunder et al., 2023). Besides antineoplastic therapy, most elderly cancer patients have accompanying chronic diseases, which add to the burden as they need to take multiple medications. It is known that about 35% of cancer patients receive polypharmacy (Datta et al., 2021; Tian et al., 2022). Patients using anticancer drugs are more prone to Adverse Drug Reactions (ADRs) due to multi-drug treatment.

In general, as many as 19.4% of hospital admissions are directly due to ADRs, 65% of which can be prevented (Lavan et al., 2019). The unwanted effects, or commonly called ADRs, especially due to chemotherapy among cancer patients, are very concerning. This negatively

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impacts the patients' quality of life and increases therapy costs. It has been found that timely reporting of chemotherapy-related ADRs and the implementation of an effective ADR monitoring system can reduce the occurrence of ADRs (Sharma et al., 2018). According to epidemiological studies, ADRs are the fourth to sixth leading cause of death, with an incidence of about 7% (Datta et al., 2021). Antineoplastic and immunosuppressive therapies cause 38% of ADRs. As many as 20.42% of hospitalized patients have to be transferred to the intensive care unit (ICU) or suffer permanent damage. The impact of ADRs on patients includes decreased quality of life, increased hospitalizations, economic burden on health management, and increased mortality rates. The estimated cost of treating ADRs is 1.76% of the total hospital budget (Datta et al., 2021). Since ADRs are unavoidable, ADR monitoring becomes an important issue to detect rare but serious ADRs in patients, thereby ensuring patient safety.

Therefore, pharmacovigilance research focused on the unwanted incidents of drug use in cancer patients, especially anticancer drugs, is very important in providing in-depth data on the safety profile of these drugs. The severity is classified using the Common Terminology Criteria for Adverse Events (CTCAE v5.0) method, allowing a good assessment of the severity of ADRs that occur and facilitating their clinical management (Freites-Martinez et al., 2021). This pharmacovigilance study is conducted for early detection of unknown side effects, detection of increased frequency of known side effects, identification of risk factors, and dissemination of information. It is important to recognize ADR patterns to improve the quality of life and reduce ADR-related hospitalization costs for cancer patients. Therefore, this study aims to understand the nature and severity of ADRs in cancer patients.

Method

Research design and method should be clearly defined**.** This study is a retrospective research based on reports of drug side effects over a period of 2 years from November 2021 to October 2023 at Dr. Saiful Anwar General Hospital (RSSA) Malang, East Java, Indonesia. Data were obtained from inpatient ESO reports during the study period. The reports were collected manually using yellow forms and digitally through an internal ADR reporting link. Inclusion criteria included the completeness of ADR reports, including patient demographic data, ADR manifestations, suspected drugs, the chronology of events and follow-up, and the outcomes of ADRs. Actions taken to address ADRs were categorized into four groups: continuing the drug with an antagonist, continuing the drug without an antagonist, stopping the drug with an antagonist, and stopping the drug without an antagonist.

The primary diagnosis and clinical manifestations of ADRs were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) System and classified according to the System Organ Class (SOC). Suspected drugs causing ADRs were categorized using The Anatomical Therapeutic and Chemical Classification System (ATC, level 2) (Giardina et al., 2018), and the severity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The obtained data were then analyzed descriptively.

Result and Discussion

Results Socio-Demographic Characteristics of Patients

The overall prevalence of adverse drug reactions (ADRs) related to drug use in cancer patients was 177 cases from November 2021 to October 2023 at Dr. Saiful Anwar General Hospital (RSSA) Malang. Of these, 74 cases (41.81%) were attributed to chemotherapy drugs. Among the patients, 99 were female (55.93%) and 78 were male (44.07%). The most common age range was 19-60 years, with 137 patients (77.40%). Studies from various countries indicate that women with cancer are 1.5 to 2 times more likely to experience ADRs and are significantly more likely to be hospitalized due to ADRs compared to men, with age and body weight not being influencing factors (Cristina et al., 2018; Özdemir et al., 2022). See table 1.

Table 1. Data on Gender and Age Distribution of Patients

Age Gender	1 - 18 th	19 - 60 th	> 60 th	Grand Total	%
Man	0	63	15	78	44.07%
Woman	1	74	24	99	55.93%
Grand Total	1	137	39	177	100.00%

Various factors related to sex (biological) and gender (psychosocial and social) may contribute to the higher incidence of ADRs in women compared to men. This condition can be caused by differences in pharmacokinetics, immunological factors, epigenetics, and hormonal factors between women and men (including the use of hormonal drugs such as oral contraceptives, and menopausal hormone replacement therapy). As a result, women have more adipose tissue than men. Differences in creatinine clearance of drugs are affected by the enzymatic activity of cytochromes (Athauda et al., 2020; Davidson et al., 2019). The pharmacokinetic effect in women is demonstrated by much higher drug concentrations in the blood and longer drug elimination times compared to men when given the same dose of drug. This may be associated

with greater plasma volume, organ perfusion, and body fat levels in Women (Franconi et al., 2013). Several pharmacokinetic analyzes have found that women have a lower elimination capacity for various anticancer drugs, including cytotoxic agents, and monoclonal antibodies (e.g., rituximab), resulting in higher plasma levels. The expression of enzymes in drug metabolism is also reported to influence sex differences. The CYP3A isoform (which accounts for approximately 50% of drug metabolism) has been reported to have 25% higher activity in women. Likewise, the ABC transporter P-glycoprotein (P-gp), which is known to be involved in drug clearance mechanisms, is known to be higher in men, so that it can explain the lower level of toxicity in these men (Yoon et al., 2021).

Clinical Characteristics of Patients

Of the 177 cases of malignant disease where ADRs occurred, 74 cases (41.80%) were caused by antineoplastic drugs. Previous research also stated that undesirable drug effects were found to be higher in cancer patients with cytostatic drugs compared to other diseases (Maharani et al., 2023). See table 2.

In Table 2 it is known that of the 177 cancer cases, the most common type of cancer that experienced ADRs wasChronic myeloid leukemia (CML) 10.17%, colorectal cancer and Non-Hodgkin Lymphoma 9.6% and Multiple myeloma 7.9%. This is in accordance with data on the drugs that most commonly cause ADRs (Table 3), namely antineoplastic agents containing platinum (Cisplatin, Carboplatin, Oxaliplatin), tyrosine kinase inhibitors (TKIs) (Afatinib, Erlotinib, Imatinib, Nilotinib) and anthracycline antibiotics (Doxorubicin, Daunorubicin). Cisplatin is a neoplastic agent containing platinum which is used in the treatment of cancer, especially in solid tumor types such as non-small cell and small cell lung cancer, esophageal and stomach cancer, head and neck cancer, genitourinary cancer and colorectal cancer (Kumar et al., 2018; Saber et al., 2018). Multiple mechanisms underlie the anticancer potential of Cisplatin, including inhibition of DNA synthesis, formation of DNA lesions and induction of mitochondrial apoptosis through the formation of DNA adducts with platinum atoms. However, cisplatinis not given alone as an anti-cancer drug due to significant side effects. Some researchers are paying attention to trials of adjuvant drugs that can be combined with Cisplatin to provide more significant antineoplastic effects and minimize the toxic effects and side effects of Cisplatin. The most common event that occurs as a result of using cisplatin is nausea/vomiting (Kumar et al., 2018) as was the case in this study (n=11). Antiemetics, for example ondansetron, are routinely given before cisplatin is infused, however, the effects of nausea and vomiting still occur, even if they are mild to moderate, which can be overcome by continuing to administer antiemetic drugs to reduce symptoms. The other most important toxicity is renal impairment (n=1) which depends on the total dose administered and can be reduced by maintaining good hydration. Tinnitus, deafness, sensory neuropathy, and hyperuricemia(Kumar et al., 2018).

Table 2. Data on the Distribution of Diagnoses for Malignant Diseases that Experience ADRs

Diagnosis	Frequency	%
Chronic myeloid leukemia (CML)	18	10.17
Colorectal Malignancy	17	9.60
Non-Hodgkin Lymphoma	17	9.60
Multiple myeloma	14	7.91
Acute myeloid leukemia (AML)	11	6.21
Pancreatic Cancer	11	6.21
Mammary carcinoma	10	5.65
Lung carcinoma	9	5.08
Osteosarcoma	8	4.52
Acute lymphoblastic leukemia (ALL)	6	3.39
Ovarian cancer	6	3.39
Nasopharyngeal Carcinoma	5	2.82
Cervical cancer	3	1.69
Hepatocellular Carcinoma	3	1.69
Hodgkin's lymphoma	3	1.69
Midline granuloma	3	1.69
Broncho Adenocarcinoma	2	1.13
Ewing Sarcoma	2	1.13
Gastric carcinoma	2	1.13
Squamous cell carcinoma (SCC)	2	1.13
Mediastinal tumors	2	1.13
Adrenal cortex carcinoma	1	0.56
Amelanotic Melanoma Malignant Cavum Oris Metastasis KGB Colli	1	0.56
Basal cell carcinoma	1	0.56
CA of unknown origin	1	0.56
Carcinoma of the ampulla of Vater	1	0.56
Endometrial cancer	1	0.56
Glioblastoma (GBM)	1	0.56
Invasive Ductal Carcinoma	1	0.56
Laryngeal cancer	1	0.56
Pituitary Macroadenoma	1	0.56
Myelodysplastic syndrome (MDS)	1	0.56
Myxofibrosarcoma (MFS)	1	0.56
ODS Pseudorefractory tumor	1	0.56
Oropharyngeal malignancy	1	0.56
Peritoneal carcinomatosis	1	0.56
Primary myelofibrosis (PMF)	1	0.56
Prostate Cancer	1	0.56
Sebaceous carcinoma	1	0.56
Spindle cell sarcoma of the mandibular os	1	0.56
Myelum Tumor	1	0.56
Undifferentiated round cell sarcomas (URCS)	1	0.56
Upper Tract Urothelial Carcinoma (UTUC)	1	0.56
Yolk sac tumor (YST)	1	0.56
Total	177	100.00

Another group that causes many ADRs is targeted cancer therapy, namely the group of tyrosine kinase inhibitors (TKIs), includingAfatinib, Erlotinib, Imatinib, and Nilotinib. TKIs have been widely used in the treatment of various hematological malignancies and solid tumors, including chronic myelogenous leukemia (CML) which is among the highest malignant diseases in which ADR occurs (10.17%), non-small cell lung cancer, stromal tumors. gastrointestinal, and HER2 positive breast cancer. TKIs are the first line treatment for CML. Due to its effects affecting many organs in the body, including the lungs, liver, digestive tract, kidneys, thyroid, blood, skin and heart, TKIs have reported an increase in the frequency of side effects caused by TKIs. Sunder et al. (2023) in several of the organs involved as reported in the results of this study, namely the digestive tract, infections and their effects on the skin, as well as their effects on the blood which causes anemia. Gastrointestinal side effects have been reported to persist for a short period of time and are largely related to TKI dose, frequency of occurrence and severity, however a reduced recurrence rate of GI side effects has been noted in cancers of solid organs such as genitourinary and lung compared with hematologic malignancies (Sunder et al., 2023). See table 3.

Table 3. Distribution of Drugs Causing ADRs and Manifestation and Severity of ADRs

MIMS Class	ATC Classification	Number of Case	%
Cytotoxic Chemotherapy	platinum-containing antineoplastic agents	27	71.57%
	cytotoxic antibiotics, anthracyclines and related substances	11	
	other antineoplastic agents	9	
	antimetabolites, pyrimidine analogues	6	
	alkylating agents, nitrogen mustard analogues	5	
	taxanes	4	
	podophyllotoxin derivatives	3	
	antimetabolites, folic acid analogues	3	
	other alkylating agents	2	
	vinca alkaloids and analogues	2	
	aromatase inhibitor	1	
Targeted Cancer Therapy	CD20 (Clusters of Differentiation 20) inhibitors	3	23.53%
	proteasome inhibitors	1	
	tyrosine kinase inhibitors (TKIs)	20	
Haematopoietic Agents	colony stimulating factors	2	1.96%
Antidotes & Detoxifying Agents	detoxifying agents used in antineoplastic treatment	2	1.96%
Cancer Hormone Therapy	gonadotropin releasing hormone analogues	1	0.98%

Table 4. Data on the Distribution of ADRs Occurring in Antineoplastic Drugs, Manifestations and the Severity of the ADRs that Occur

Antineoplastic Agents	System Organ Class (SOC}	CTAE Terms	Manifestation of Suspected ADRs				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
5-fluorouracil	Blood and lymphatic system disorders	Febrile neutropenia			1		1
	Gastrointestinal disorders	Mucositis oral	1				
Afatinib	Gastrointestinal disorders	Mucositis oral		1			
		Diarrhea			3		
	Infections and infestations	Papulopustular rash		1			
	Skin and subcutaneous tissue disorders	Mucositis oral		1			
		Rash acneiform	1				
		Urticaria		2			
		Nail discoloration	1				
		Alopecia	1				
Anastrozole	Nervous system disorders	Phantom pain		1			
Carboplatin	Metabolism and nutrition disorders	Hypokalemia			2		
	Renal and urinary disorders	Acute kidney injury			2		
Cisplatin	Blood and lymphatic system disorders	Febrile neutropenia			1		
	Gastrointestinal disorders	Nausea		1			
		Nausea, Vomiting	2	5			
	Nervous system disorders	Peripheral sensory neuropathy	2	1			
	Renal and urinary disorders	Acute kidney injury			1		
Dacarbazine	Blood and lymphatic system disorders	Febrile neutropenia			1		

Antineoplastic Agents	System Organ Class (SOC}	CTAE Terms	Manifestation of Suspected ADRs				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Gastrointestinal disorders	Dyspepsia, Nausea, Vomiting		1			
Daunorubicin	Blood and lymphatic system disorders	Anemia			1		
		Febrile neutropenia				1	
Docetaxel	Gastrointestinal disorders	Diarrhea		1			
Erlotinib	Skin and subcutaneous tissue disorders	Urticaria		1			
Etoposide	Blood and lymphatic system disorders	Anemia			1		
	Gastrointestinal disorders	Nausea	1				
Filgrastim	General disorders and administration site conditions	Injection site reaction		1			
	Musculoskeletal and connective tissue disorders	Myalgia		1			
Hydroxycarbamide	Blood and lymphatic system disorders	Anemia		1	2		
	Skin and subcutaneous tissue disorders	Urticaria		1			
Imatinib	Blood and lymphatic system disorders	Anemia			1		
	Gastrointestinal disorders	Nausea	1				
		Nausea, Vomiting	1	5			
		Diarrhea		1			
Melphalan	Blood and lymphatic system disorders	Anemia		1			
Nilotinib	Skin and subcutaneous tissue disorders	Urticaria		1			
Oxaliplatin	Blood and lymphatic system disorders	Febrile neutropenia			1		
	Gastrointestinal disorders	Nausea, Vomiting		1			
	Nervous system disorders	Peripheral sensory neuropathy	1	1			
	Renal and urinary disorders	Urinary incontinence		2			
Rituximab	Gastrointestinal disorders	Nausea	1				
	Skin and subcutaneous tissue disorders	Rash maculo-papular			1		
		Urticaria		1			
Temozolomide	Gastrointestinal disorders	Constipation	1				
		Vomiting	1				
	Respiratory, thoracic and mediastinal disorders	Hiccups	1				
Doxorubicin	Cardiac disorders	Left ventricular systolic dysfunction			1		
		Ventricular arrhythmia		1			
	Gastrointestinal disorders	Nausea	1				
		Nausea, Vomiting		1			
	Nervous system disorders	Peripheral sensory neuropathy		1			
	Skin and subcutaneous tissue disorders	Urticaria		1			
Paclitaxel	Nervous system disorders	Peripheral sensory neuropathy		1			
Vincristine	Blood and lymphatic system disorders	Thrombotic thrombocytopenic purpura					1
	Nervous system disorders	Peripheral sensory neuropathy		1			
Cytarabine	Blood and lymphatic system disorders	Febrile neutropenia				1	

Afatinib is an irreversible epidermal growth factor receptor gene (ErbB) TKI. The ADRs reactions observed in the study were most often related to skin reactions including acne (n=1), canker sores (n=1), skin rash (urticaria) (n=2), alopecia (n=1), and changes in nail color. (n=1) which occurred with a mild degree (scale 1 and 2). It was stated in previous studies that the most frequently observed adverse reactions during afatinib therapy included skin rash/acne eruption, stomatitis/mouth ulcers, diarrhea, paronychia, and

pruritus (Cheng et al., 2024; Edwards et al., 2018). These dermatological effects are common because EGFR plays an important role in skin physiology. Inhibition of EGFR causes a series of cellular events that result in skin effects such as rash, dry skin, pruritus, and inflammation of the nail/periungual tissue (Califano et al., 2015). Even though it occurs in a mild to moderate degree and can be managed with administration of antagonists, this can have an impact on quality of life and increase the risk of non-compliance (Charles et al., 2016). Diarrhea (n=3) was the most common ADRs occurring with EGFR TKI therapy, and is thought to be caused by several factors, including excessive chloride secretion resulting in secretory diarrhea (Hirsh et al., 2014).

Diarrhea usually occurs during the early weeks of afatinib treatment so patients must be closely monitored, educated early on regarding dietary management including avoiding dairy products, raw vegetables, caffeine, alcohol, fiber and spicy foods, and eating small portions more frequently, and given antimotility drugs to treat diarrhea (Edwards et al., 2018; Hirsh et al., 2014). Patients with persistent diarrhea may also require temporary discontinuation of treatment. If grade 2 diarrhea persists for >48 hours, intravenous fluids/electrolytes need to be given to increase water intake to prevent dehydration. Meanwhile, for early/mild stages of oral stomatitis/mucositis (n=1) due to afatinib, or damage to the mucosal lining of the gastrointestinal tract, it can be treated with topical management, for example topical steroids, and maintaining good oral hygiene (brushing teeth regularly, flossing). with floss and gargle); avoiding hot, sour, spicy, or salty foods; and drink lots of water (Choi et al., 2012; Edwards et al., 2018; Patil et al., 2015). Patients who are given mouthwash containing topical steroids should also be educated and monitored regarding the risk of developing stomatitis (Patil et al., 2015). Oral candidiasis can be treated using topical medications or systemic antifungal agents (to a greater degree). Pain and difficulty swallowing may occur if mucositis extends to the back and beyond the oral cavity. Examination of the patient's nasal mucosa if nosebleeds occur while taking afatinib may reveal nasal vestibulitis and topical mupirocin administration may be considered in this condition (Ruiz et al., 2015). Providing education to patients is very necessary.

Severity Assessment of Adverse Drug Reactions

Tables 4 and 5 show the incidence of ADRs reported by patients, which occurred during and after chemotherapy. Digestive disorders are still the largest manifestation of ADRs found (37.04%) including nausea and vomiting, diarrhea, mouth ulcers and difficulty defecating, blood disorders (18.52%), skin disorders (14.81%), digestive disorders. Nerve disorders (11.11%), and kidney disorders (7.41%) were the main complaints most frequently reported as undesirable drug effects in patients administered antineoplastics. There were 17 (20.99%) manifestations of stage 1 ADRs, 40 (49.38%) manifestations of stage 2 ADRs, 20 (24.69%) manifestations of stage 3 ADRs, 2 (2.47%) manifestations of stage 4 ADRs and 2 (2.47%) manifestations of stage 5 ADRs There were 2 manifestations of ADRs that caused death, namely Fluorouracil (5-FU) which caused febrile neutropenia (n=1) and vincristine which was thought to cause thrombocytopenia purpura (n=1). Milder degrees (grade 4) occurred with manifestations of febrile neutropenia (n=2) caused by Daunorubicin and Cytarabine. Fluorouracil (5-FU) as a single agent therapy or in combination with other anticancer drugs, is used in the treatment of various malignant diseases in humans, including gastrointestinal cancer, breast cancer, head and neck cancer. 5-FU is a highly toxic drug with a narrow therapeutic index.

Severe hematological toxicity, gastrointestinal complications may occur with the use of 5-FU despite administration to the right patient and appropriate dose adjustment. It is known that the variability of 5-FU toxicity between patients is wide and that 5-FU toxicity can be predicted based on dose, schedule and route of administration (Mugada et al., 2017). 5-FU-induced colonic toxicity has the potential to be severe, especially in colonic malignancies or other malignancies that receive 5-FU-based therapy. 5-FU-based combination regimens are also associated with severe gastrointestinal toxicity and high mortality rates (Mugada et al., 2017). Several studies reported that partial or complete DihydroPyrimidine Dehydrogenase (DPD) deficiency was associated with an increased risk of grade IV neutropenia after 5-FU administration.

Chemotherapy with cytotoxic agents suppresses cancer cells and healthy cells that divide rapidly such as skin, bone marrow, mucous membranes, etc. Among these cells, hematological toxicity due to chemotherapy is feared to affect hemoglobin levels, blood clotting mechanisms and the body's defense mechanisms (Korucu et al., 2018; Monestime et al., 2021). Decreased neutrophil levels may resulta serious threat to patients undergoing chemotherapy that can make them susceptible to the risk of infection. The Infections Diseases Society of America (IDSA) has published guidelines for the treatment of patients with febrile neutropenia by administering intravenous antibiotics during treatment (Mugada et al., 2017). In other research on head and neck cancer, it was stated that to reduce the incidence of febrile neutropenia, filgrastim prophylaxis was administered. The frequency of side effects, the amount of granulocyte colony-stimulating factor (G-CSF) used, the cost of treatment and the length of stay were significantly reduced by administration of

filgrastim (Wasano et al., 2017). So, in the case of chemotherapy with a regimen containing 5-FU given to patients with head and neck cancer, filgrastim can be considered as primary prophylaxis against febrile neutropenia.

Table 5. Organs Affected by ADRs, Number of Occurrences and Severity of ADRs

System Organ Class (SOC)	CTAE Terms	Manifestation of Suspected ADRs						
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	%
Gastrointestinal disorders	Constipation	1					30	37.04
	Dyspepsia, Nausea, Vomiting		1					
	Mucositis oral	1	1					
	Nausea	4	1					
	Nausea, Vomiting	3	12					
	Vomiting	1						
	Diarrhea		2	3				
Blood and lymphatic system disorders	Anemia		2	5			15	18.52
	Febrile neutropenia			4	2	1		
	Thrombotic thrombocytopenic purpura					1		
Skin and subcutaneous tissue disorders	Mucositis oral		1				12	14.81
	Rash acneiform	1						
	Rash maculo-papular			1				
	Urticaria		7					
	Nail discoloration	1						
	Alopecia	1						
Nervous system disorders	Peripheral sensory neuropathy	3	5				9	11.11
	Phantom pain		1					
Renal and urinary disorders	Acute kidney injury			4			6	7.41
	Urinary incontinence		2					
Cardiac disorders	Left ventricular systolic dysfunction			1			2	2.47
	Ventricular arrhythmia		1					
Metabolism and nutrition disorders	Hypokalemia			2			2	2.47
General disorders and administration site conditions	Injection site reaction		1				1	1.23
Infections and infestations	Papulopustular rash		1				1	1.23
Musculoskeletal and connective tissue disorders	Myalgia		1				1	1.23
Psychiatric disorders	Insomnia		1				1	1.23
Respiratory, thoracic and mediastinal disorders	Hiccups	1					1	1.23
		17	40	20	2	2	81	100.00

Thrombotic thrombocytopenic purpura is a potentially life-threatening condition. Giving plasma exchage has been proven to reduce the death rate from 90% to 10%-20%, but around 40% of patients experience recurrence, and the results can be fatal in patients who are difficult to cure (Öngören et al., 2018). Thrombocytopenia is a common problem in cancer patients and occurs in 10-68% of patients with solid tumors or hematological cancer who experience thrombocytopenia caused by chemotherapy drugs (Gao et al., 2023; Soff et al., 2022). In evaluating cancer patients with thrombocytopenia, it is necessary to assess other causes of thrombocytopenia, including immunologic thrombocytopenia, coagulopathy, infection, thrombocytopenia due to drug reactions, post-transfusion purpura, and thrombotic microangiopathy (Kuter, 2022). The incidence of chemotherapy-induced thrombocytopenia varies greatly depending on the treatment used; the highest rates of this condition were associated with gemcitabine and platinum-based regimens. Each chemotherapy drug differs in how it causes thrombocytopenia: alkylating agents affect stem cells, cyclophosphamide affects later megakaryocyte progenitors, bortezomib prevents platelet release from megakaryocytes, and some treatments promote platelet apoptosis. Thrombopoietin is a key regulator of platelet production. In many studies, recombinant thrombopoietin increased platelet counts, reduced the need for platelet transfusions, reduced the duration of thrombocytopenia, and allowed maintenance of

chemotherapy dose intensity (Soff et al., 2022). Chemotherapy dose reduction and platelet transfusion remain the mainstay of treatment for patients with thrombocytopenia. Vincristine given has been proven to be able to treat recurrent thrombotic thrombocytopenic purpura (Öngören et al., 2018). So in this case, the incidence of thrombotic thrombocytopenic purpura may be caused by other drugs.

This research was conducted retrospectively using data from previous ADRs reports. Therefore, the limitation of this research is that only available data archives with all their limitations can be analyzed. The majority of ADRs reports collected are incomplete and lack detail in explaining the chronology of ADRs, making causality analysis difficult to carry out. In addition, not all drugs coadministered with suspected drugs are reported, because most reporters only report suspected drugs, making it almost impossible to analyze polypharmacy and possible drug interactions associated with ADR events. Apart from that, there are also reports that are not reported because there is important data that is not written down, for example the manifestation of ADRs experienced by patients. In addition, there is the possibility that there are other reporting accounts outside the Pharmacy Unit, so that ADRs reporting is not detected. Therefore, improvements and adjustments need to be made to internal reporting links so that the collected ADRs reports are more complete, so they can be analyzed comprehensively. In addition, it is hoped that health workers will play an active role as professional health service providers in detecting and reporting ADRs so that they can collect more post-marketing drug monitoring data and improve drug safety monitoring in Indonesia.

Conclusion

Reporting of ADRs at this hospital has gone quite well, especially for patients with malignancies which require service providers to be more careful with everything given to the patient. Even though the number of ADRs reports is still quite low, each report can help in the evaluation and management of subsequent ADRs. Most cases of ADRs are experienced by women and the productive age group. The group of drugs that causes the most ADRs isantineoplastic agents containing platinum, tyrosine kinase inhibitors (TKIs) and anthracycline antibiotics.The manifestations of ADRs are dominated by gastrointestinal disorders, blood and lymphatic disorders, and skin & subcutaneous tissue disorders. Severe ADRs occur with manifestations of febrile neutropenia and thrombocytopenia purpura which, if prompt and appropriate management is not carried out, can cause death. Reporting of ADRs in this study occurred on spontaneous effects that occurred in patients. For long-term effects or requiring special monitoring, a special reporting system and broader evaluation is needed. The incidence of ADRs, whether mild or moderate, must still be evaluated because management that is not fast and appropriate can have an impact on the patient's quality of life. Patient education (pre-treatment), good communication, assessment of awareness of ADRs, and responsiveness (including supportive care measures and appropriate dose modifications), enable patients to experience clinical benefits for managing ADRs and continuing therapy.

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Author Contributions
The following statements should be used Conceptualization, D.W.; C.M.S.; B.S. contributed to the data collection process, data processing, article writing.

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Conflicts of Interest
The authors declare no conflict of interest.

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