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Onkoloji Hastalarında İlaç Etkileşimlerinin İncelenmesi

Investigation of Drug-Drug Interactions in Oncology Patients

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ÖZ

Giriş: Ek hastalığa sahip kanser hastaları onkolojik tedavilerinin yanında, diğer hastalıklara özgü farklı farmakolojik gruplarda düzenli ilaç kullanmaktadır. Bu durum morbidite ve mortalite artışına yol açan potansiyel ilaç-ilaç etkileşimlerine (PİİE) yol açmaktadır. Çalışmada amaç onkoloji hastalarında görülen PİİE'yi göstermektir.

Yöntem: Medikal Onkoloji kliniğinde kanser tanılı, ilk kez kemoterapi alan ve ilaç protokolü değiştirilmiş 250 hastanın dosyası incelenmiştir. Hastaların kullandığı ilaçlar PİİE açısından Medscape ve Drugs.com online veri tabanlarına ait 2020 yılı verileriyle incelenmiştir. PİİE, klinik önem açısından majör, orta ve minör olarak sınıflandırılırken, mekanizması açısından ise farmakodinamik ya da farmakokinetik etkileşimler olarak sınıflandırılmıştır. Sonrasında potansiyel olarak majör etkileşim gösteren ve QT mesafesini uzatan ilaçlar listelenmiştir.

Bulgular: Çalışmada, polifarmasi oranı yüksekti. Çalışmaya dahil edilen hastaların %55,6'i erkek, %44,4'ü kadın hastalardan oluşmaktaydı. PİİE görülen hasta sayısı Medscape ve Drugs.com'a göre sırasıyla; 223 (%85,2);238 (%95,2) idi. Bu etkileşimlerde major etkileşim görülen hasta sayısı ve oranı Medscape ve Drugs.com'a göre sırasıyla 28 (%11,2), 67 (%26,8) idi. Toplam, 99 adet ilaç çifti QT aralığını uzatmaktaydı. Medscape'e göre; 52 (%20,8) hastada 77 adet, Drugs.com'da ise 136 (%54,4) hastada toplam 298 adet QT mesafesini uzatan ilaç etkileşim çifti vardı. Ek hastalık sebebiyle kullanılan ilaç sayısındaki artışın PİİE'yi anlamlı düzeyde arttırdığı görüldü (P<0,05).

Sonuç: Çalışmaya dahil edilen hastalarda görülen majör PİİE oranları, potansiyel QT mesafesini uzatan ilaçların kullanım sayıları diğer çalışmalarla karşılaştırıldığında benzerdir. Ancak, özellikle bazı PİİE'ye neden olabilecek ilaçların sık yazıldığı reçete edildiği ve bu durumun önlenebilir olduğu görülmüştür. Bu ilaçlar reçete edilirken dikkatli davranılmalı ve alternatif bir tedaviyle değiştirilemediği durumlarda klinisyen tarafından yakın takibi yapılmalıdır.

Anahtar Kelimeler: potansiyel ilaç-ilaç etkileşimleri, medikal onkoloji, uzun QT, polifarmasi

ABSTRACT

Objective: Cancer patients with comorbidities often require multiple pharmacological treatments in addition to their oncological therapies. This situation can lead to potential drug-drug interactions (PDDIs), increasing morbidity and mortality. The study aims to identify PDDIs in oncology patients.

Method: The records of 250 cancer patients from a Medical Oncology clinic who were either receiving chemotherapy for the first time or had a change in their drug protocol were reviewed. The medications were analyzed for PDDIs using 2020 data from the Medscape and Drugs.com databases. PDDIs were classified by clinical significance (major, moderate, minor) and mechanism (pharmacodynamic, pharmacokinetic). Drugs with major interactions and those prolonging the QT interval were listed.

Results: A high rate of polypharmacy was observed. Of the patients, 55.6% were male, and 44.4% were female. PDDIs were identified in 223 (85.2%) and 238 (95.2%) patients according to Medscape and Drugs.com, respectively. Major interactions were found in 28 (11.2%) and 67 (26.8%) patients, respectively. A total of 99 drug pairs prolonged the QT interval. According to Medscape, 77 interactions were seen in 52 (20.8%) patients, while Drugs.com identified 298 interactions in 136 (54.4%) patients. An increase in the number of medications for comorbidities significantly raised the PDDI risk (P<0.05).

Conclusion: The rate of major PDDIs and the number of QT-prolonging drugs in this study are comparable to other studies. However, certain frequently prescribed drugs pose preventable risks. Caution is needed when prescribing these medications, and close monitoring by clinicians is advised when alternatives are unavailable.

Keywords: potential drug-drug interactions (PDDIs), medical oncology, long QT, polypharmacy

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INTRODUCTION

Potential drug-drug interactions (PDDIs), which occur when interacting medications are administered to a patient concurrently, are preventable conditions associated with serious and potentially fatal side effects (1).

One of the most vulnerable patient groups to PDDIs is oncology patients. Chemotherapy drugs often have a narrow therapeutic index. When drug-drug interactions (DDIs) are introduced into an already challenging treatment course due to severe adverse reactions, it can cause significant complications. Considering that oncology patients often use numerous medications in addition to chemotherapy, PDDIs can potentially lead to a greater increase in morbidity and mortality in this population (2–4).

Studies investigating medications prescribed to oncology patients in various countries have shown varying rates of at least one PDDIs present in patient medications (27-58%). While there is no specific standard for evaluating the significance of these interactions, most are considered clinically important (2,5,6). In fact, some studies estimate that DDIs are responsible for death in up to 4% of cancer patients (1,7). These findings further highlight the importance of PDDIs awareness.

Drug interactions encompass more than just interactions between medications. There are four main categories: drug-drug interactions, drug-disease interactions, nutrient-drug interactions, and drug-herbal product interactions (8).

Drug-drug interactions, a specific type of adverse drug reaction, occur when one medication alters the effect of another. While some interactions may lead to a synergistic effect and enhanced therapeutic benefit, others can result in toxicity or unwanted side effects. These undesirable effects can range from treatment failure and increased adverse events to severe drug reactions and even mortality (9). There are three main mechanisms by which drug-drug interactions can occur: pharmaceutical, pharmacokinetic, and pharmacodynamic (10).

Pharmaceutical interactions, also known as incompatibilities, occur when medications are physically mixed together during administration, particularly in parenteral (injectable) therapies. This can lead to precipitation or inactivation of one or both drugs (11).

Pharmacokinetic drug interactions occur at the levels of absorption, distribution, metabolism, and excretion of the target drug. The effect of the interacting drug may vary in parallel with its plasma concentration and occurs within the body (12).

Pharmacodynamic interactions refer to the effects of drugs on each other's pharmacological actions. These interactions occur at the organ and receptor levels, and the concentration of the drugs themselves remains unchanged (12).

The most common clinical results of DDI are Serotonin Syndrome and long QT interval. Serotonin syndrome is a drug reaction caused by a pharmacological interaction that occurs when drugs that increase serotonin levels are taken together (13). Long QT syndrome, on the other hand, is a risk factor for fatal ventricular arrhythmias. It is often observed with syncope and sudden cardiac deaths. Torsades de pointes type arrhythmias are most commonly caused by long QT interval (14).

While we anticipate that proactive identification of potential PDDIs can reduce mortality and morbidity, it is important to acknowledge that not every PDDI is clinically significant. Studies suggest that only a portion of PDDIs are clinically relevant and necessitate intervention (15). In other words, when a PDDI is detected, close patient monitoring may be sufficient without necessarily discontinuing treatment.

The primary objective of this study is to enhance physician awareness of drug-drug interactions. The secondary objective is to determine the prevalence of potential drug-drug interactions within the oncology department of our hospital. Based on existing research on drug interactions conducted worldwide and within our country, the study will evaluate the PDDIs status in oncology patients. Ultimately, it aims to contribute to the identification of PDDIs in oncology and raise awareness about drug interactions in this patient population.

MATERIALS AND METHODS

This retrospective, descriptive study was conducted in collaboration with the Department of Medical Oncology and the Department of Medical Pharmacology at … University Faculty of Medicine and approval for the study was granted by the Gazi University Clinical Research Ethics Committee on August 19, 2020 (decision number: 25901600-604.01.01-19).

The study population comprised patient files from the Medical Oncology outpatient clinic at … University Faculty of Medicine Hospital during the first three months of 2020.

Assuming a 20% frequency, a 5% deviation value, and a design effect (DEFF) of 1, the sample size was calculated using the unknown population size formula ($n = t^2 * p * (1-p) / d^2$) with a 95% confidence level ($\alpha = 0.05$). This calculation yielded a sample size of 246. To ensure adequate representation, 250 patient files were reviewed.

Patient files included in the study met the following criteria: First-time chemotherapy recipients, experiencing a change in their drug regimen.

Demographic information, cancer type, medications used, and any additional diagnoses were obtained from the patient files. Medications were categorized into four groups: Chemotherapy drugs, premedication therapy drugs, other drugs registered with the Anatomical Therapeutic Chemical Classification System (ATC), herbal medicinal products and herbal teas.

Two online databases, Medscape and Drugs.com, were chosen for potential drug interaction evaluation due to their accessibility and potential for capturing a wider range of interactions reported in the literature and the datasets utilized in this analysis were extracted from these two databases, those pertaining to the calendar year 2020 (16,17). Medscape was selected based on its demonstrated ability to reflect clinically relevant drug interactions (18), while Drugs.com was chosen for its high sensitivity (19).

Potential drug interactions were classified according to their clinical significance (major, moderate, minor) and mechanism (pharmacokinetic or pharmacodynamic). Interactions were assessed within and between medication categories. Drugs with the potential for major interactions and long QT interval were then identified.

Patient files were reviewed again to assess the documented clinical impact of any major interactions. However, the file review did not yield sufficient information to evaluate clinically significant PDDIs.

Statistical Analysis

Descriptive statistics were used to describe patient demographics, cancer types, additional diseases, number of medications, and characteristics of drug interactions. The relationship between cancer types and total drug interactions was evaluated statistically using Jamovi, a statistical software package. The Kruskal-Wallis test was employed to analyze the non-normally distributed data on the total number of interactions identified on both Medscape and Drugs.com across groups with more than three categories, considering the number of additional diseases and total medications used by patients. Jamovi was also used for this analysis.

RESULTS

A retrospective analysis was conducted on the medical records of 250 patients. The sample population consisted of 55.6% males and 44.4% females (Table 1). Comorbidities including diabetes mellitus, hypertension, and coronary artery disease were present in a subset of patients, with varying prevalence rates (Table 1). The most prevalent primary cancer diagnoses among men were lung cancer (30.2%, n=42), followed by gastrointestinal cancer (21.6%, n=30), and pancreatic cancer (8.6%, n=12). In women, the most common primary cancer diagnoses were breast cancer (35.1%, n=39), followed by gastrointestinal cancer (15.3%, n=17), and lung cancer (11.7%, n=13). The average number of medications used per patient was 9.22 ± 3. Based on medication use, patients were categorized into three groups: those using 5 or fewer medications (9.2%, n=23), those using 6-10 medications (57.2%, n=143), and those using 11 or more medications (33.6%, n=84). Due to the low prevalence (6 patients), data on herbal medication use was excluded from the analysis. (Table 1)

Inconsistencies were observed between the utilized databases regarding the clinical significance (major, moderate, minor) of potential drug interactions. To assess these discrepancies, evaluations of potential moderate and major interactions were compared. Interactions designated as major in one database but undetected (even at a minor level) in the other database were documented numerically. This analysis identified a total of 916 discrepancies between the databases in terms of clinical significance (mean difference = 3.66 interactions per patient).

An analysis using the Medscape database revealed that 85.2% (n=223) of patients had at least one PDDIs. Among these patients, 11.2% (n=28) had at least major PDDIs. Ten of these majör PDDIs were pharmacokinetic interactions, while the remaining 27 were pharmacodynamic interactions. The Medscape database identified major PDDIs in 12 patients with lung cancer, 9 with breast cancer, 3 with gastrointestinal cancer, and none with pancreatic cancer. Notably, 13 patients with other cancer diagnoses also exhibited major PDDIs.

An analysis of the Drugs.com database revealed a high prevalence of PDDIs in the study population. PDDIs were observed in 95.2% (n=238) of patients. Among these, 26.8% (n=67) were classified as major PDDIs.

Of the major PDDIs, the majority (92%) were pharmacodynamic interactions, with only 7 classified as pharmacokinetic interactions.

Table 1. General Information About Gender, Comorbidities, Drug use, Comorbidities and Herbal Product use of Patients

n=250	**Total Number**	**Incidence Percentage**		
Gender	**Male**	139	55.6%	
	Woman	111	44.4%	
Age	**Mean**	**Median**	**Min**	**Max**
	60,1	61,0	23	90
Additional types of diseases	**DM**	40	16.0%	
	HT	102	40.8%	
	CAD	55	22.0%	
Number of Comorbidities		**Total Number**	**Incidence Percentage**	
	0	124	49.6%	
	1	63	25.2%	
	2	55	22.0%	
	3	8	3.2%	
Types of Cancer		**Total Number**	**Incidence Percentage**	
	Lung	55	22.0%	
	Gastrointestinal system	42	16.8%	
	Breast	39	15.6%	
	Pancreas	18	7.2%	
	Other	96	38.4%	
Information on the Number of Drugs Used	**Median**	**Average ± SE**	**Min**	**Max**
	9	9,22	1	18
Use of Herbal Medicinal Product or Herbal Tea	**Number of Drugs Used**	**Total Number**	**Incidence Percentage**	
	0	244	97.6%	
	1	5	2.0%	
	2	1	0.4%	

Min: Minimum, Max: Maximum, DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Artery Disease, SE: Standard Error

The analysis of major PDDIs by cancer type revealed no statistically significant difference ($p>0.05$) between cancer types and the overall frequency of PDDIs. Specifically, major PDDIs were identified in patients with gastrointestinal cancer (n=24), lung cancer (n=21), pancreatic cancer (n=13), breast cancer (n=12), and other unspecified cancers (n=29). (Table 2), (Figure 1)

This analysis revealed a positive correlation between the number of medications and the incidence of PDDIs. Patients prescribed eleven or more medications exhibited a significantly higher prevalence of major PDDIs compared to those taking fewer medications ($p < 0.05$). Similarly, a statistically significant association ($p < 0.05$) was observed between the increasing number of co-morbidities and the overall number of PDDIs identified in both databases.

Furthermore, an analysis of drug class interactions across both databases highlighted a propensity for PDDIs to occur between chemotherapeutic agents and premedication drugs, as well as between premedication drugs and other medications used concomitantly (Table 3)

This study investigated the prevalence of potential drug-drug interactions (PDDIs) within a large patient cohort. Folinic acid and 5-fluorouracil (5FU) emerged as the most frequently encountered PDDI, identified in 27 patients. This interaction, however, was considered therapeutically desirable. Granisetron-tramadol (n=8) and granisetron-escitalopram (n=6) pairs represented the subsequent most frequent potential interactions. Notably, granisetron, dexamethasone, tramadol, acetylsalicylic acid, escitalopram, moxifloxacin, and amiodarone were identified as the medications most commonly involved in major PDDIs.

Furthermore, an analysis was conducted to evaluate drugs known to long QT interval. Medscape data revealed that the granisetron-5FU combination was the most prevalent PDDI associated with long QT interval, affecting 20.8% (n=52) of patients. Drugs.com data indicated a similar trend, with this PDDI identified in 54.4% (n=298) of patients. Additionally, granisetron, famotidine, oxaliplatin, and doxorubicin were identified as frequently co-prescribed medications. Among these potential interactions, granisetron-oxaliplatin (n=42), granisetron-famotidine (n=36), oxaliplatin-5FU (n=26), and granisetron-doxorubicin (n=23) pairs were the most frequently observed.

Electrolyte imbalances were investigated as another potential PDDIs category. Medscape data revealed a prevalence of 10.4% (n=26 patients, average value 0.22) and Drugs.com data indicated a prevalence of 74.8% (n=187 patients, average value 1.90). (Table 4)

Table 2. Total Number and Rates of PDDIs Seen in Databases and Number and Proportions of Patients Seen

	Number of PDDIs with Patients		Number of PDDIs			
	Medscape Database	Drugs.com Database	Medscape Database		Drugs.com Database	
Total PDDIs	223 (85.2%)	238 (95.2%)	1068		1735	
Major PDDIs	28 (11.2%)	67 (26.8%)	37	FC 10	99	FC 7
			(3.46%)	FD 27	(5.70%)	FD 92
Moderate PDDIs	193 (87.2%)	235 (94.0%)	690	FC 386	1370	FC 428
			(64.60%)	FD 304	(78.96%)	FD 942
Minor PDDIs	144 (57.6%)	135 (54.0%)	341		266	
			(31.92%)		(15.33%)	

PDDIs: Potential Drug Drug Interactions, FC: Pharmacokinetic interaction, FD: Pharmacodynamic interaction

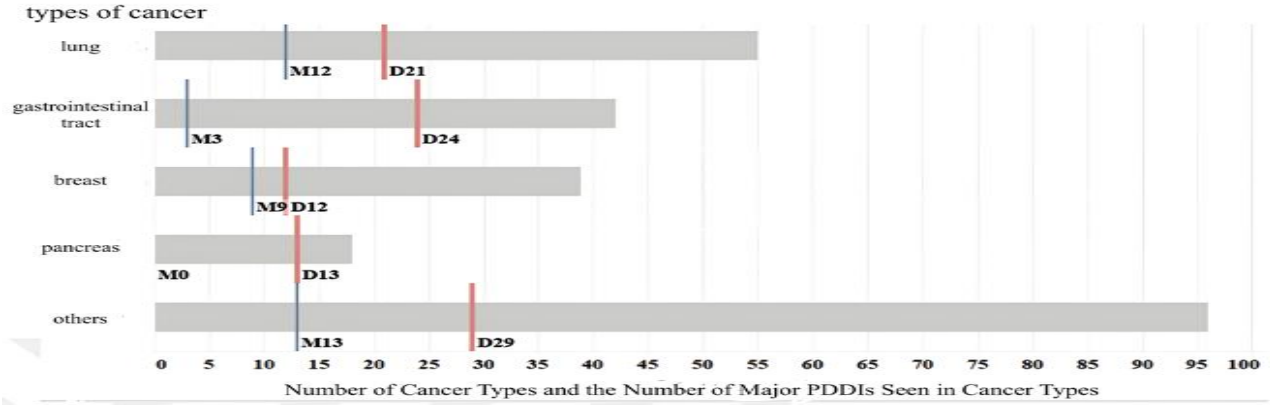

Figure 1. Distribution of Major Interactions in Databases by Cancer Types

(M: Medscape,, D: Drugs.com. The horizontal gray bars show the number of cancer species, and the red lines above it give the number of major PDDIs.)

Table 3. Number of Patients with PDDIs and Distribution of Total Major PDDIs According to Databases

	Medscape		Drugs.com	
	Number and percentage of people with PDDIs	**Total number of major PDDIs**	**Number and percentage of people with PDDIs**	**Total number of major PDDIs**
PDDIs among chemotherapeutics themselves	66 (26.4%)	122	137 (48.8%)	234
PDDIs between chemotherapeutics and premedication drugs	**130 (52.0%)**	**159**	**166 (66.4%)**	**222**
PDDIs between chemotherapeutics and other ATC-registered drugs used by the patient	47 (18.8%)	57	108 (43.2%)	229
PDDIs between premedication drugs	**1 (0.4%)**	**1**	**2 (0.8%)**	**2**
ATC used by the patient with premedication drugs PDDIs among other registered drugs	115 (46.0%)	217	158 (63.2%)	459

PDDIs: Potential Drug Drug Interactions, ATC: Anatomical Therapeutic Chemical Classification System

Table 4. Drugs and Drug Groups Causing of the Long QT Interval

Drugs that long QT interval	Number of occurrences in interaction pairs
Granisetron	26
Antacids (Omeprazole, Lansoprazole, Pantoprazole,Esomeprazole, Famotidin)	23
SSRI, SNRI (Escitalopram, Citalopram, Sertraline, Mirtazapine)	20
COPD Drugs (Formoterol, Albuterol, Budesonide)	18
Diuretics (Hydrochlorothiazide, Furosemide, Indapamide)	12
Hypertension Drugs (Alfuzosin, Nebivolol, Metoprolol)	11
Tramadol	9

DISCUSSION

This study investigated the prevalence of polypharmacy and PDDIs in the participating patients. We found that a significant proportion of patients (96.8%) used more than five medications, with 44% exceeding eleven drugs. The average number of medications used per patient was nine. These findings align with the existing literature, which reports an average medication usage of nine in similar patient populations (2,20,21). The analysis of PDDIs revealed a high prevalence, with 85% of patients exhibiting potential interactions in the Medscape database and 95% in the Drugs.com database.

While the Drugs.com database identified a higher number of PDDIs, it is essential to consider its broader access to four distinct databases and larger infrastructure (22). However, some studies suggest that the Medscape database offers a more clinically relevant representation of interactions (18). This study is limited in its ability to definitively comment on this aspect due to the absence of data on actual clinical outcomes related to PDDIs.

The current literature lacks a definitive source for the specific incidence of PDDIs. However, several studies report similar or even higher rates of total PDDIs compared to our findings, while others show a lower prevalence.

Similarly, a cohort study in India involving 126 cancer patients demonstrated a total PDDIs rate of 97.6%, despite a higher average patient age and lower medication usage (23). For instance, a study conducted in Pakistan with 150 breast cancer patients reported a total PDDIs rate of 92%. This discrepancy might be attributed to the patient population being limited to breast cancer patients and potential variations arising from the use of different databases (24).

Unlike the present study, a study conducted in India reported a total PDDIs rate of 47%, while a French study found a rate of 26% (25,26). These variations might be attributed to differences in the number of medications used or database discrepancies. Two studies by Leeuwen et al. investigated PDDIs in cancer patients, identifying them in 46% and 58% of participants, respectively. These studies employed the 'Facts and Comparisons®: Drug Reference Resource' databases. Notably, the average number of medications used by patients in our study (7) is higher compared to the 5 reported in the Leeuwen et al. studies. This difference in medication usage is likely a contributing factor to the observed discrepancies in PDDIs rates (2,3).

The current study demonstrated a significant positive correlation between the number of medications used and total PDDIs. Patients taking eleven or more medications exhibited a marked increase in major interactions. Additionally, a rise in the number of co-existing diseases was

associated with an increase in PDDIs ($p < 0.05$). These findings are consistent with previous research (23,24,27,28), which similarly reported a positive association between the number of medications and PDDIs, as well as an increased PDDIs rate with a higher number of co-morbidities. Therefore, patients on polypharmacy and with multiple chronic conditions warrant particular vigilance regarding major drug interactions.

No statistically significant association was observed between cancer types and PDDIs in the present study. However, Alkan et al. (27) identified a link between lung cancer and other cancer types in their literature review. Conversely, Leeuwen et al. (3) reported that breast cancer exhibited a higher PDDIs rate compared to genitourinary cancers, with the three most prevalent types being breast, gastrointestinal, and genitourinary cancers. Interestingly, the current study also identified lung, gastrointestinal, and breast cancer as the top three types. These discrepancies might be due to variations in patient population distribution across studies. Consequently, a thorough evaluation of medications for PDDIs is crucial for all cancer types.

Consistent with existing literature, the present study found a higher prevalence of pharmacodynamic interactions compared to pharmacokinetic interactions. Metoclopramide and granisetron were identified as the most frequently interacting drugs in previous studies regarding PDDIs. While granisetron emerged as a prominent drug for PDDIs in this study, metoclopramide was not among the frequently interacting medications. Similar to the current study, antiemetic agents, proton pump inhibitors, systemic corticosteroids, and antimetabolites were frequently implicated in PDDIs (23,29).

Two databases, Medscape and Drugs.com, report varying prevalence of major PDDIs, with 11.2% and 26.8%, respectively. The most common major PDDI involves folinic acid and 5-fluorouracil, where careful monitoring for myelotoxicity, mucositis, and diarrhea is crucial (20). Additionally, major PDDIs were identified with granisetron, tramadol, and escitalopram, potentially leading to serotonin syndrome and long QT interval.

Literature reports on major PDDI prevalence range from 8% to 62.2% (28,30,31). These variations are attributed to factors such as the database used, patient demographics, disease profiles, and the number of medications employed.

Long QT interval, a potential consequence of some PDDIs, can lead to arrhythmias and even death. The Medscape database identified a potential for long QT interval in 20.8% of patients, compared to 54.4% in the Drugs.com database. Common drug classes involved include antiemetics (granisetron), chemotherapeutic agents (doxorubicin, oxaliplatin), a proton pump inhibitor (famotidine), and pain relievers (tramadol). Literature findings (23,31,32) align with the Medscape data for these specific drug interactions.While the Drugs.com database appears more sensitive in detecting PDDIs, its real-world clinical impact remains unclear. Further research is needed to determine which database offers the most practical utility in daily clinical practice. Across drug groups, the present study revealed interaction rates that differed from previous findings. The interaction rate for antineoplastic agents was around 20% in this study, compared to both databases.

However, Bibi et al. (2021) reported a higher rate of 32%. Similarly, the ratio of antineoplastic-premedication interactions to all interactions in this study (20-30%) diverged from Bibi et al.'s finding of 62.9%. Conversely, the ratio of antineoplastic-other drug interactions to all interactions was approximately 15% in this study, which is higher than the 5% reported by Bibi et al. These findings suggest that the current study might have overlooked interactions between antineoplastic drugs and other drug types while focusing on PDDIs between antineoplastics and premedication drugs (24).

A forward-looking intervention study conducted at the Erasmus MC Cancer Institute identified 120 potentially clinically significant interactions out of 603 potential interactions detected. Interventions were implemented for 81 patients (15). If this study had been designed as a forward-looking intervention study, comparisons with online resources like Medscape and Drugs.com suggest that interventions or close follow-up proposals should have been made for 37 and 99 major PDDIs, respectively.

CONCLUSION

There may be significant discrepancies between online databases. Therefore, researchers should consult more than one source when examining drug interactions.

Although our study did not find a clear correlation between the number of additional diseases and the likelihood of drug interactions, patients with multiple chronic conditions and those taking several medications (polypharmacy) showed a higher number of potential interactions. This suggests that these patients require closer attention during medication prescription or initiation of chemotherapy.

The type of cancer did not significantly influence the number of drug interactions. However, when examining interactions between chemotherapy and pre-medication drugs, it is crucial to consider all medications, vitamins, herbal products, and nutritional supplements used by the patient. In our study, herbal medicine use was uncommon. Nevertheless, it is important to inquire about herbal tea and supplement use during a chemotherapy patient's medical history (anamnesis).

While the rates of potentially critical drug interactions were lower compared to some other studies, there were still preventable occurrences. This is an important consideration when prescribing medication or starting chemotherapy. Drug groups with a high number of major interactions include chemotherapeutics (Cisplatin, doxorubicin), antiemetics (Granisetron, ondansetron), pain medications (Tramadol), and antidepressants (Escitalopram, citalopram). Special attention should be paid to these medications, and consultation with the Medical Pharmacology Department may be necessary.

Despite careful protocols, there is a risk of overlooking missed drug interactions, particularly those that could lead to serotonin syndrome. This is especially concerning for the elderly patient population, who often have multiple chronic conditions, particularly heart-related diseases. Drugs that potentially prolong QT interval can be particularly dangerous for these patients. Our study found a high number of interactions with drugs that extend the QT interval.

These drugs include granisetron, chemotherapeutics (Oxaliplatin, doxorubicin), gastric acid regulators (Omeprazole, lansoprazole, pantoprazole, esomeprazole, famotidine), SSRIs and SNRIs (Escitalopram, citalopram, sertraline, mirtazapine), COPD medications (Formoterol, albuterol, budesonide), diuretics (Hydrochlorothiazide, furosemide, indapamide), antihypertensive drugs (Alfuzosin, nebivolol, metoprolol), and tramadol medications that prolong QT interval. Clinicians should exercise particular caution when prescribing these drugs and closely monitor patients when alternative treatments are unavailable.

A significant limitation of this study is its retrospective nature. We believe this research lays the groundwork for future prospective, multi-centered studies with treatment interventions. These studies could involve a broader patient population (wider universe) and patient follow-up, ultimately leading to improved patient care in this area.

Limitations of the Study

This study is subject to several limitations inherent to its retrospective design. Ideally, a prospective study would serve as a preliminary investigation for a multi-center trial. Such a prospective design would allow for patient treatment, follow-up, and recruitment from a wider patient population (broader universe). Due to information deficiencies in the files, we were unable to collect data on the clinical manifestations of the identified potential interactions between medications and herbal products (PDDIs). Additionally, the single-center nature of the study limits our ability to generalize the findings to a broader population. It is also possible that patients may have unintentionally omitted reporting herbal medicinal products, teas, or over-the-counter medications due to forgetfulness or a reluctance to disclose such information.

Ethics Committee Approval: Gazi University Clinical Research Ethics Committee -19.08.2020 -25901600-604.01.01-19.

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Informed Consent: Sınce our study ıs retrospectıve, patıent consent was not obtaıned.

REFERENCES

1. Buajordet I, Ebbesen J, Erikssen J, Brørs O, Hilberg T. Fatal adverse drug events: the paradox of drug treatment. J Intern Med. 2001;250(4):327-341.
2. Van Leeuwen RWF, Swart EL, Boven E, Boom FA, Schuitenmaker MG, Hugtenburg JG. Potential drug interactions in cancer therapy: a prevalence study using an advanced screening method. Ann Oncol. 2011;22(10):2334–2341.
3. Van Leeuwen RWF, Brundel DHS, Neef C, van Gelder T, Mathijssen RHJ, Burger DM, et al. Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer. 2013;19;108(5):1071–1078.
4. Mathijssen RHJ, Sparreboom A, Verweij J. Determining the optimal dose in the development of anticancer agents. Nat Rev Clin Oncol. 2014;11(5):272–281.
5. Riechelmann RP, Tannock IF, Wang L, Saad ED, Taback NA, Krzyzanowska MK. Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst. 2007;99(8):592-600.
6. Riechelmann RP, Zimmermann C, Chin SN, Wang L, O'Carroll A, Zarinehbaf S, et al. Potential drug interactions in cancer patients receiving supportive care exclusively. J Pain Symptom Manage. 2008;35(5):535–543.
7. Ebbesen J, Buajordet I, Erikssen J, et al. Drug-related deaths in a department of internal medicine. Arch Intern Med. 2001;161(19):2317-2323.
8. Arslan D, Tural D, Akar E. Herbal administration and interaction of cancer treatment. J Palliat Med. 2013;16(11):1466–1476.
9. Roblek T, Vaupotic T, Mrhar A, Lainscak M. Drug-drug interaction software in clinical practice: a systematic review. Eur J Clin Pharmacol. 2015;71(2):131–142.
10. Van Leeuwen RWF, van Gelder T, Mathijssen RHJ, Jansman FGA. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol. 2014 ;15(8):e315-326.
11. Büyükokuroğlu ME, Tanyeri P, Keleş R. İlaç-İlaç Etkileşimleri Konusunda Farkındalık. Online Türk Sağlık Bilimleri Dergisi. 2019;30;4(3):377–391.
12. Katzung BG, editor. Basic & clinical pharmacology. Fourteenth edition. New York Chicago San Francisco Athens London Madrid Mexico City Milan New Delhi Singapore Sydney Toronto: McGraw-Hill Education; 2018. 1146–1162 p. (A Lange medical book).
13. Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003;96(9):635–642.
14. Witchel HJ, Hancox JC. Familial and acquired long qt syndrome and the cardiac rapid delayed rectifier potassium current. Clin Exp Pharmacol Physiol. 2000 Oct;27(10):753–766.
15. Van Leeuwen RWF, Jansman FGA, van den Bemt PMLA, de Man F, Piran F, Vincenten I, et al. Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions. Ann Oncol. 2015 May;26(5):992–997.
16. Suriyapakorn B, Chairat P, Boonyoprakarn S, Rojanarattanangkul P, Pisetcheep W, Hunsakunachai N, et al. Comparison of potential drug-drug interactions with metabolic syndrome medications detected by two databases. PLoS One. 2019;14(11):e0225239.
17. Janković SM, Pejčić AV, Milosavljević MN, Opančina VD, Pešić NV, Nedeljković TT, et al. Risk factors for potential drug-drug interactions in intensive care unit patients. J Crit Care. 2018;43:1–6.

18. Kara E, Tecen-Yücel K, Özdemir N, İnkaya AÇ, Bayraktar-Ekincioğlu A, Demirkan K, et al. Yoğun Bakım Hastalarında Antibiyotiklerin Diğer İlaçlarla Etkileşimlerinin Değerlendirilmesi. STED / Sürekli Tıp Eğitimi Dergisi. 2019;28(6);404–409.

19.Bossaer JB, Thomas CM. Drug Interaction Database Sensitivity With Oral Antineoplastics: An Exploratory Analysis. J Oncol Pract. 2017;13(3):e217–222.

20.Ismail M, Khan S, Khan F, Noor S, Sajid H, Yar S, et al. Prevalence and significance of potential drug-drug interactions among cancer patients receiving chemotherapy. BMC Cancer. 2020;20(1):335.

21.Karakoç MD. Kanser Hastalarında Polifarmasi ve İlaç Etkileşimleri. Adnan Menderes Üniversitesi Sağlık Bilimleri Fakültesi Dergisi. 2022;31;6(1):31–42.

22.Özonuk E, Yılmaz M. Relationship Between Health Literacy and Compliance with the Treatment Among Individuals with Type 2 Diabetes Mellitus. J Educ Res Nurs. 2019;16(2):96–103.

23.Ramasubbu SK, Mahato SK, Agnihotri A, Pasricha RK, Nath UK, Das B. Prevalence, severity, and nature of risk factors associated with drug-drug interactions in geriatric patients receiving cancer chemotherapy: A prospective study in a tertiary care teaching hospital. Cancer Treat Res Commun. 2021;26:100277.

24.Bibi R, Azhar S, Iqbal A, Jabeen H, Kalsoom UE, Iqbal MM, et al. Prevalence of potential drug-drug interactions in breast cancer patients and determination of their risk factors. J Oncol Pharm Pract. 2021;27(7):1616–1622.

25.Daggupati SJV, Saxena PUP, Kamath A, Chowta MN. Drug-drug interactions in patients undergoing chemoradiotherapy and the impact of an expert team intervention. Int J Clin Pharm. 2020;42(1):132–140.

26.Lachuer C, Perrin G, Chastel A, Aboudagga H, Thibault C, Delanoy N, et al. Pharmaceutical consultation to detect drug interactions in patients treated with oral chemotherapies: A descriptive cross-sectional study. Eur J Cancer Care (Engl). 2021;30(3):e13396.

27.Alkan A, Yasar A, Karci E, Koksoy EB, Ürun M, Senler FC, et al. Severe drug interactions and potentially inappropriate medication usage in elderly cancer patients. Support Care Cancer. 2017;25(1):229–236.

28.Hong S, Lee JH, Chun EK, Kim KI, Kim JW, Kim SH, et al. Polypharmacy, Inappropriate Medication Use, and Drug Interactions in Older Korean Patients with Cancer Receiving First-Line Palliative Chemotherapy. Oncologist. 2020;25(3):e502–511.

29.Moghaddas A, Adib-Majlesi M, Sabzghabaee AM, Hajigholami A, Riechelmann R. Potential drug-drug Interactions in hospitalized cancer patients: A report from the Middle-East. J Oncol Pharm Pract. 2021;27(1):46–53.

30.Domínguez-Alonso JA, Conde-Estévez D, Bosch D, Pi-Figueras M, Tusquets I. Breast cancer, placing drug interactions in the spotlight: is polypharmacy the cause of everything? Clin Transl Oncol. 2021;23(1):65–73.

31.Khan Q, Ismail M, Khan S. Frequency, characteristics and risk factors of QT interval prolonging drugs and drug-drug interactions in cancer patients: a multicenter study. BMC Pharmacol Toxicol. 2017;1;18(1):75.

32.Ergun Y, Yildirim Ozdemir N, Toptas S, Kurtipek A, Eren T, Yazici O, et al. Drug-drug interactions in patients using tyrosine kinase inhibitors: A multicenter retrospective study. J BUON. 2019;24(4):1719–1726.