Eur J Clin Oncol 2020; 2(1): 1-7.

European
Journal of Clinical Oncology

Research

Drug-Drug Interaction of Oral Antineoplastic Agents in the Cancer Patient

Lara Martín Rizo[1*], Marta Sánchez Gómez-Serranillos [2], Marcelo Domínguez Cantero[3], Luis Carlos Fernández Lisón[1], Irene Iglesias Peinado[2], María Pilar Gómez-Serranillos Cuadrado[2]

[1]Department of Pharmacy, University Hospital Cáceres, Madrid, Spain

[2]Department of Pharmacology, Pharmacognosy and Botany, Complutense University, Madrid, Spain

[3]Department of Pharmacy, University Hospital Puerto Real, Madrid, Spain

[*]Correspondence should be addressed to Lara Martín Rizo, Department of Pharmacy, University Hospital HM Sanchinarro, Madrid, Spain, Tel: +32 646306155; Email: lara.martinrizo@gmail.com

Received: 6 May 2020 • Accepted: 17 May 2020

ABSTRACT

Background: The aim is to describe the potential interactions between oral antineoplastic agents and concomitant medication. Previous studies proved that oral antineoplastic agents are associated with significant drug-drug interactions.

Methods: The retrospective observational study to detect the potential interactions drug between oral antineoplastic agents and concomitant medication. All drug interactions detected between concomitant medication and oral antineoplastic agents were recorded. All potential interactions were classified by database as C (monitor therapy), D (consider therapy modification) or X (avoid combination) risk level. The analysis was carried out with three different databases. A descriptive analysis was conducted, including into account the demographic and clinical data, as well as the drug most commonly prescribed in the analyzed treatment.

Results: A total de 315 drug-drug interactions were detected in 222 treatments. The average drug-drug interactions per patients relative to the total was 1,4. Most of the patients included had at least one potential interaction between oral antineoplastic agents and concomitant treatment. The interactions were resolved by monitoring or dose adjustment.

Most part of interactions detected was of pharmacokinetic type (71.1%). For drug-drug interactions with antineoplastic agents, 180 interactions (57%) were classified as category C, 58 interactions (18.4%) as category D and 77 interactions (24.6%) as category X.

Conclusion: The study proved that oral antineoplastic agents can increase the risk of drug-drug interaction. The sensitivity observed when detecting an interaction is different between the databases consulted. It thus highlights the importance of determining the clinical relevance of oral chemotherapy drug-drug interactions. For this, multidisciplinary team's participation is essential.

Keywords: Oral antineoplastic agent, Interactions, Oral chemotherapy, Pharmacokinetic, Concomitant medication.

INTRODUCTION

Cancer is the universal name for a large group of disease, defined as an uncontrolled proliferation of abnormal cells, and invasion of the body by spreading to nearby or distant organs or tissues. Chemotherapy is the main treatment for cancer and benefits patients in the form of decreased relapse and metastasis and longer overall survival [1].

For several reasons, oncology patients in particular need intensive medication monitoring and counselling. Elderly patients often use more drugs as a result of comorbidities. This increases the risk of drug-related problems with anticancer drugs in these patients [2].

The expansion of oral chemotherapy has grown exponentially, with over 55% of chemotherapy agents approved in the past decade pertaining to oral chemotherapy. However, the rapid growth in the approval and clinical use of oral chemotherapy agents in de United States has not been accompanied with the appropriate safety measures commonly utilized with parenteral chemotherapy [3].

The oral administration introduces the possibility of interactions related to absorption and improper co-

administration with other drugs, issues that are not critical when using intravenous chemotherapy [4].

For patients, using such agents is attractive partly because of perceived greater convenience. However, the use of many of these agents presents multiple challenges, including novel toxicity profiles, increases risk for drug interactions, high cost, and potential challenges with treatment adherence [5].

Most oral antineoplastic drugs approved since 2010 are associated with multiple clinically significant drug-drug interactions (DDI). The risk for these DDI is increased by concurrent medications prescribed for preexisting chronic diseases common in the aging oncology population, and by the complexity associated with obtaining these expensive oral chemotherapy agents through specific pharmacy restriction programs [6].

DDI occur when a patient´s pharmacological or clinical response to the drug is modified by administration or co-exposure to another drugs [7].

Recent studies suggest that the risk of DDI is common, in particular since the advent of oral anticancer agents. DDI are either pharmacokinetic or pharmacodynamics. Most pharmacokinetic interactions may result from inhibition or induction of cytochrome P450 (CYP) enzymes, or from transport proteins [8].

Cancer patients are a population susceptible to DDI when receiving antineoplastic agents associated with supportive treatment and other drugs to treat comorbidities. Narrow therapeutic margin drugs linked to organic deterioration and altered pharmacokinetics; affect the metabolism and renal excretion processes [9].

A recent study revealed that co-prescription of drugs that induce or inhibit metabolic pathways used by tyrosine kinase inhibitors (TKIs) was high. Overall co-prescribing rates for DDI drugs that may decrease TKIs effectiveness ranged from 23-57% while co-prescribing rates with drugs that may increase TKI toxicity ranged from 24%-74% [7].

Sing et al. described cancer patients are at a higher risk of DDI, which can be attributed to their compound course of therapy as well as altered pharmacokinetic and pharmacodynamics [10].

Knowledge and the proper management of drug interactions can improve the safety and effectiveness of treatments. The studies carried out present disparate methodologies, so the incidence of interactions, their severity and risk reduction strategies are poorly defined [9]. Pharmacy services are essential in preventing adverse effects and potential interactions in cancer patients [11].

Gómez et al. describe that the pharmaceutical intervention the absolute risk of suffering an adverse event caused by a drug interaction can be reduced by 25.9% [12].

Several online/mobile databases with DDI features are available for clinician use. However, authors concluded that the drug information databases vary in their ability to answer proposed questions in each clinical area [13].

The principal objective is to describe the potential interactions, pharmacokinetic and pharmacodynamics, between oral antineoplastic agents and concomitant medication.

METHODS

Observational retrospective study of potential drug interactions between oral antineoplastic agents and concomitant medication during the medical treatment of oncological inpatients. The study included all patient >18 years diagnosed solid tumour treatment oral antineoplastic agents between 2016-2018. Exclusion criteria were: Patients without concomitant medication, patients without information electronic medical history or patient with haematological diseases.

The electronic medical history (JARA®) and the electronic medical record (Farmatools®) were used to collect demographic and clinical data.

Each prescribed medication was recorded according to its active ingredient and subsequently evaluated. If a drug contained two or more active ingredients, each active ingredient was separately evaluated. The anatomical-therapeutic-chemical (ATC) classification of drugs was used to classify active ingredients.

We recorded the total number of drugs prescribed for each treatment, disaggregating the number of antineoplastic and non-antineoplastic drugs. Antineoplastic agents or drugs were defined as those used for the treatment of malignant cancer, regardless of its mechanism of action [9].

All prescription lines were analyzed according to different databases (Medinteract®, Bot-plus® and Lexicom®). All drug interactions detected between concomitant medication and oral antineoplastic agents were recorded. All potential interactions were classified by database with a level of risk C (monitor therapy), D (consider therapy modification) or X (avoid combination) risk level. Severe interaction was defined as that which may cause risk to the patients.

Drug-drug interactions are classified into two types: pharmacokinetic or pharmacodynamics. Pharmacokinetic interactions arise when absorption, distribution, metabolism or elimination of the involved drugs are altered, leading to changes in the amount and duration of drug availability at receptor sites.

Pharmacodynamics interactions usually refer to an interaction in which active compounds change each other´s pharmacological effect. This effect can be synergistic, additive or antagonistic [14].

A descriptive analysis was conducted of the demographic and clinical data and the drugs most commonly prescribed in the analysed treatment were conducted.

RESULTS

A total of 467 patients were initially identified as eligible; of these, 61 were excluded because they had not prescribed concomitant medication.

Finally, we analysed 406 patients, 60% man, and average age was 65.8 years (range from 25 to 89 years). The most frequent tumour location was digestive (63%), followed by gynecological (11%), genitourinary (11%) and pulmonary (8.4%).

The median number of drugs tested per treatment was 6.3 (2-16). The most commonly used antineoplastic drugs were capecitabine (51%), trifluridine/tipiracile (7.2%), regorafenib, abiraterone and temozolomide (4%), everolimus (3.4%) or vinorelbine (3%). Other antineoplastic agents were prescribed once each during the study period, mostly ITK. **Table 1** summarizes the general characteristics of patients.

Table 1: General characteristics.

Characteristics	Frequency	Percentage (%)
Male	241	60
Age	65.8	
Oncology diagnoses		
Digestive cancer	256	63
Gynecological cancer	45	11
Genitourinary cancer	45	11
Pulmonary cancer	34	8.4
Brain cancer	16	4
Skin cancer	10	2.6
Antineoplastic agents		
Abiraterone	16	4
Afatinib	5	1.2
Alectinib	1	0.2
Axitinib	1	0.2
Capecitabine	211	51
Ceritinib	1	0.2
Crizotinib	2	0.5
Dabrafenib	10	2,4
Enzalutamide	11	2.7
Erlotinib	3	0.7
Everolimus	14	3.4
Gefitinib	8	2
Imatinib	6	1.5
Lapatinib	4	1
Nintedanib	4	1
Olaparib	4	1
Palbociclib	3	0.7
Pazopanib	11	2.7
Regorafenib	16	4
Sorafenib	6	1.5
Sunitinib	5	1.2
Temozolomide	16	4
Topotecan	5	1.2

Trametinib	6	1.5
Trifluridine/Tipiracile	30	7.2
Vinorelbine	13	3

Of the 406 patients analyzed, 184 did not involve DDI. Of the remaining 222 patients (55%), there were 315 potential DDI. The median number of DDI per patients relative to the total was 1.4. In most patients one or two interactions were detected (91%).

Most of the patients included had at least one potential interaction between oral antineoplastic agents and concomitant treatment. The interactions are resolved by monitoring or dose adjustment.

For DDI with antineoplastic agents, 180 interactions (57%) were classified as category C, 58 interactions (18.4%) as category D and 77 interactions (24.6%) as category X.

The main mechanisms of interaction were pharmacokinetic factors (71.1%) followed by pharmacodynamic factors (28.9%). Of the pharmacokinetic interactions, 50.8% occurred at absorption level while 20.8% were metabolic. **Table 2** shows the general characteristics of the interactions.

Table 2: General characteristics of the interactions.

Characteristics	Frequency	Percentage (%)
Interactions	315	
Median number of DDI/patient	1.4	
Number of interactions		
One interaction	155	69.8
Two interactions	48	21.6
Three interactions	14	6.3
Four or more interactions	5	2.25
Severity of interactions		
Category C	180	57
Category D	58	18.4
Category X	77	24.6
Type of interactions		
Pharmacokinetic	224	71.1
Pharmacodynamic	91	28.9
Interactions according to the database		
Database 1	97	30.8
Database 2	281	89.2
Database 3	205	65

DDI were analyzed using three different databases. Depending on the database between 97 or 281 interactions are detected.

The three databases show agreement regarding the antineoplastic agents involved in the interactions. However, the concomitant medication involved in the interactions is more variable. Interactions with metamizole or allopurinol are only detected by one of the databases.

The interactions classified as category X summarizes in **Table 3.** Metamizole interacts with antineoplastic agents such as capecitabine, sorafenib or trifluridine/tipiracile.

Interactions between proton pump inhibitors (PPIs) and antineoplastic agents such as dabrafenib, lapatinib or pazopanib are also described in category X.

The oral antineoplastic agents most commonly involved in DDI were capecitabine (59.6%), enzalutamide (11.5%), pazopanib (5.4%) and dabrafenib (5%). No interactions were

recorded in the case of alectinib, axitinib, nintedanib, topotecan or trametinib.

Table 3: Interactions classified category.

Interactions	Frequency	Percentage (%)
Capecitabine-Acenocumarole	7	9
Capecitabine-Allopurinol	11	14.3
Capecitabine Metamizole	30	39
Crizotinib-Fentanyl	1	1.3
Dabrafenib-Omeprazole	6	7.8
Dabrafenib-Pantoprazole	1	1.3
Enzalutamide-Fentalyl	1	1.3
Erlotinib-Omeprazole	1	1.3
Imatinib-Metamizole	1	1.3
Pazopanib-Atorvastatin	2	2.6
Pazopanib-Rabeprazole	1	1.3
Pazopanib-Omeprazole	5	6.5
Pazopanib-Pantoprazole	3	3.9
Sorafenib-Metamizole	1	1.3
Temozolomide-Metamizole	2	2.6
Trifluridine/tipiracile-Metamizole	4	5.2

The drug most involved in DDI were PPIs (53%), analgesics (15.2%), antihypertensive (6%), statins (5.7%) antidepressant (4.1%) or gout drugs (3.5%). **Table 4** shows the antineoplastic agents and concomitant medication involved of interactions.

Table 4: Agents antineoplastic and treatment domiciliary involved DDI.

Characteristics	Frequency	Percentage (%)
Antineoplastic agents involved DDI		
Abiraterone	6	1.9
Capecitabine	186	59.6
Dabrafenib	16	5
Enzalutamide	37	11.5
Everólimus	5	1.5
Other ITK	36	11.5
Pazopanib	17	5.4
Regorafenib	2	0.6
Temozolomide	4	1.2
Trifluridine/Tipiracilo	4	1.2
Vinorelbine	2	0.6
Concomitant medication involved DDI		
Analgestic/Opiods	48	15.2
Oral anticoagulants	10	3.2
Antiepileptics	3	1

Antidepressanst	13	4.1
Gout drugs	11	3.5
Antihypertensive	19	6
Corticosteroids	7	2.3
Statins	18	5.7
Antidiabeticts	6	2
PPIs	166	53
Other	14	4

DISCUSSION

Patients with cancer are more at risk for DDI. It has been shown that 20%-30% of adverse drug reactions can be attributed to drug interactions [2].

The study of Pimienta et al. detected 180 potential DDI and 63% of the patients had at least one potential DDI [15]. Leeuwen et al. detected that 46% of the patients of your study were exposed at least one DDI [16].

In the present study, more than half of the patients included in the study had at least one potential interaction between oral antineoplastic agents and concomitant treatment. The interactions are resolved by monitoring or dose adjustment.

Capecitabine is the drug involved in most DDI, followed by enzalutamide or pazopanib. The concomitant treatment involved in the interactions is all support medications in cancer patients. Liñara et al. studied that the concomitant medication most commonly involved in DDI were analgesics, antihypertensive and antidepressants, followed by PPIs or antidiabetics [14]. Riu-Viladoms et al. determined that the pharmacological group most involved in the interactions was PPIs [17].

Although it is difficult to compare the results with those of other studies, because of the different methodologies used and the different settings analyzed, the concomitant treatment involved DDI in our study resembles the results of Liñara et al. or Rui-Viladoms et al.

As was seen in our study, the drug group most involved in DDI was PPIs (53%). These interactions are the results of absorption disorders. In contrast to the situation observed with intravenous drugs, DDI occurring at absorption level are particularly important in oral administration and can result in increased or decreased treatment efficacy [18]. There are several oral antineoplastic agents that interact with acid-suppressing agents. This interaction was demonstrated for erlotinib, dasatinib and gefitinib [4].

Van Leeuwen et al. determined that anticoagulant, which are routinely used for the treatment of thrombosis, are highly prone for DDI with anticancer drug. In this interaction between anticoagulant and anticancer drug, the anticoagulant effect may be altered, and a clinical intervention is recommended [19]. In our study were detected interactions between capecitabine and anticoagulant, classified into category X.

The sensitivity observed when detecting an interaction is different between the databases consulted. This fact was exposed in the works of Fernández de Palencia et al. or other similar studies where significant differences were observed between the databases used [20]. Díaz Carrasco et al. show that a striking difference in the identification of several DDI between databases. Most of these DDIs commonly involved metamizole [9]. As was seen in our study, interacts between antineoplastic agents with metamizole or allopurinol with capecitabine were only detected by a single database. Both conclusions show the differences between databases and the importance of using several of them and comparing the results.

Leeuwen et al. concluded the additional search in the databases is expected to increase the number of detected drug interactions in the study population [21].

However, it thus highlights the importance of determining the clinical relevance of oral chemotherapy DDI. This would be of significant value to prescribers when making treatment decisions, especially in older patients whose treatment choices may be limited due to multiple comorbid conditions and patient preferences [4].

For this, multidisciplinary team's participation is essential and software applications are gaining particular importance in the daily clinical practice. The joint collaboration of oncologist and pharmacists involved in the care of patients with oral chemotherapy could prevent and detect more DDI. In fact, Leeuwen et al concluded that, next to the intervention already carried out by the oncologist, interventions were carried out based on recommendations of clinical pharmacologist [19].

The main limitation of this study is that the results are based upon treatment evaluations and no patient outcomes have been followed over time to detect clinical consequences of interactions.

Conclusion

The oral anticancer medications have an increased risk for drug-drug interactions. The sensitivity observed when detecting an interaction is different between the databases consulted. It thus highlights the importance of determining the clinical relevance of oral chemotherapy drug-drug interactions. For this, multidisciplinary team's participation is essential.

Contribution of author

Martin Rizo L, Domínguez Cantero M, Sánchez Gómez-Serranillos M, Gómez-Serranillos Cuadrado MP coordinated the data-analysis and contributed to the writing of the manuscript.
Martín Rizo L and Gómez-Serranillos Cuadrado MP are corresponding to the methods and experimental section.

Martín Rizo L designed the research strategy and prepared the study.

Fernández Lison LC, Iglesias Peinado I contributed to the review and editing of the manuscript.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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