# Potential Drug Interactions between Oral Antineoplastic Agents and Opioid Analgesics

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***Abstract***. *Oral antineoplastic drugs use has been gaining more importance due to its multiple benefits and the introduction of new molecules with new mechanisms of action. Opioids are often conjugated with antineoplastic therapy, however, this association brings possible drug interactions. Cytochrome P450 is responsible for the metabolization of a great part of drugs on the market. Identifying, explaining, and assessing the severity of possible drug interactions between oral antineoplastic agents and opioid analgesics were the aims of this investigation. A cross-sectional observational study was developed. Drugs selected in FHNM, were combined one by one in the Micromedex database. Twenty-three interactions were found with different types of grades of evidence and severity, and six were explained. Procarbazine was the oral antineoplastic with the highest number of possible interactions, while the opioid was buprenorphine. It's important to monitor drug interactions in cancer patients considering the serious consequences that may arise from these.*

**Keywords.** Antineoplastic agents, opioid analgesics, drug interactions, cancer therapy, pain management

University of Maribor Press

DOI https://doi.org/10.18690/um.3.2022.12
ISBN 978-961-286-658-7

# 1 Introduction

## 1.1 Oral Antineoplastic Agents

As a result of the increasing number of people diagnosed with cancer, as well as, the development of new agents with different mechanisms of action, the use of oral antineoplastic agents has been increasing [1], [2]. A primary goal of treatment with antineoplastic agents is to treat cancer, increase life expectancy and bring quality of life [1].

By using oral chemotherapy, multiple benefits have been demonstrated when compared with traditional methods, in particular for quality of life [2]. This is thanks to the administration at home by the patient, thus avoiding constant hospital visits for treatments, as well as, decreasing the dependence on caregivers and also maintaining a relatively constant level of medication throughout the treatment period [2]. Furthermore, the use of these agents eliminates the risk of developing infections derived from IV access of intravenous chemotherapy, because this isn´t an invasive method [3].

There are four phases in the cell cycle: the pre-synthetic phase or G1, the phase in which DNA synthesis takes place or phase S, the post-synthesis phase or G2, and mitosis phase or phase M [4]. Traditional oral antineoplastic agents damage cancer cells and interfere with their cellular division [5]. Most of these agents can be distinguished by the cell cycle phase in which they interfere. Etoposide acts in the G2 phase, and inhibits topoisomerase II, preventing cells from entering the M phase of the cell cycle where mitosis normally occurs [5]. Antimetabolites, such as methotrexate, interfere in the S phase of the cell cycle, more precisely in the synthesis of nucleic acids, replacing them with purines or pyrimidines or by inhibiting enzymes important in the synthesis of nucleic acids [5]. In the case of alkylating agents such as procarbazine, these are not cell cycle specific, because they act on DNA, replacing an alkyl group with a hydrogen atom, which results in cell death [5].

Nevertheless, the use of these drugs raises an issue: potential drug-drug interactions concerning drug pharmacokinetics. This may have serious consequences which can lead to serious adverse events or a decrease in effect [2].

## 1.2 Opioid Analgesics

Cancer patients are commonly polymedicated, with treatment for comorbidities or with adjuvant therapy to give better support to antineoplastic treatment. Because most of the time these patients look for different clinicians and don't inform them about the drugs that they are using, being polymedicated, as well as age, is a risk factor for potential drug-drug interactions [3].

Pain is a common symptom associated with cancer and its treatments. In a study of more than 5.000 adults, 56% of cancer patients suffer from moderate to severe pain [6]. Its prevalence is greater the more advanced the state of cancer [6]. That is why it is important to look for solutions to limit pain linked to cancer.

Opioids are frequently used to manage pain associated with cancer, as they are indicated for the treatment of moderate to severe pain [6]. Some adverse effects like sedation, nausea/vomiting, and constipation are frequently felt due to the use of opioid analgesics [7]. Moreover, respiratory depression can also occur [7]. Opioids connect to opioid receptors. There are mu (μ), kappa (κ), and delta (δ) opioid receptors [8]. Mu receptors are those that, when activated by stimulation of a ligand, cause supraspinal analgesia, respiratory depression, euphoria, and sedation, being located in the brainstem or medial thalamus. These are responsible for opioid dependence [8]. Kappa receptors are located in the spinal cord, and brainstem, and when stimulated are at the origin of the actions such as spinal analgesia, sedation, dysphoria, and also dependence [8]. Finally, delta receptors are distributed throughout the brain and whose stimulation causes psychomimetic and dysphoric symptoms [8]. This connection triggers neuronal depolarization [9]. Opioids can be grouped according to their action mechanism, in: agonists (act by connecting to the opioid receptors and this group includes morphine, codeine, and fentanyl), partial agonists (where buprenorphine is included), agonists-antagonists (those who have partial antagonist activity in mu receptors) and antagonists (naltrexone acts like a competitive antagonist in mu receptors) [8].

A process that drugs go through to be eliminated from the body is called metabolism [10]. When metabolism is altered by another drug, this can lead to an increasing concentration of the drug that wasn't properly metabolized, which leads to toxic effects or a reduction in its concentration to complete the objective of its administration [10].

Opioid metabolism is divided into two phases: phase I is responsible for oxidation or hydrolysis by CYP3A4 or CYP2D6, while in phase II there is an increase in hydro-solubility for renal excretion [9], [10]. Drugs such oxycodone, fentanyl, hydrocodone, and methadone are metabolized by CYP3A4, while codeine and tramadol suffer metabolization by CYP2D6. Morphine, hydromorphone, and oxymorphone have minimal or no phase I metabolism [9], [10].

### 1.3 Drug Interactions

Drug interactions are defined as drug combinations that can lead to therapeutic failure and potential adverse events that wouldn't occur if the drugs were administered individually [1].

The potential drug-drug interactions can be distinguished between, pharmacokinetics, pharmacodynamics, and pharmaceutical [11]. Pharmaceutical interactions occur when two incompatible chemical products are associated [11]. Pharmacokinetics interactions are associated with absorption, distribution, metabolism, and elimination of the drug or association [7], [11]. These are frequently related to drug metabolization by cytochrome P450 enzymes, through inhibition or induction of CYP isoenzymes and consequently, blood concentration and anticancer agent toxicity can be altered [11]. The pharmacokinetic interactions can also result in P-glycoprotein inhibition, which can affect antineoplastic bioavailability [11]. When the interactions are the result of the mechanism of action of the drugs involved they are classified as pharmacodynamics [11]. This can lead to synergisms, antagonisms, or additions resulting in beneficial actions or the opposite [11].

Most antineoplastic agents are metabolized by CYP450, acting as inhibitors or inducers of one or more isoenzymes [3], [12]. Cytochrome P450 is responsible for most of the drug's metabolism. Several drug interactions result from alterations of CYP450 metabolism [13].

Drugs can act like CYP450 inhibitors or inducers. Inhibitors are responsible for blocking the metabolic activity of one or more enzymes belonging to the CYP450 enzyme complex, and the effects of this inhibitory action usually occur immediately [13]. Inducers are responsible for increasing the synthesis activity of enzymes belonging to CYP450, however, unlike inhibitors, the increase in enzyme activity does not occur immediately [13]. A drug can be metabolized by an enzyme and in the same way, inhibit the same enzyme [13].

The CYP3A4 isoenzyme is the most related to pharmacokinetic interactions [12]. The main isoenzyme responsible for the metabolism of oral anticancer drugs is CYP3A4 and because these drugs can act like inhibitors or inducers, the concomitant use of oral antineoplastic agents and opioid analgesics can alter opioid metabolism, resulting in higher or reduced concentrations, respectively, of opioids [9], [10] The P-glycoprotein has a high expression in tissues responsible for absorption, distribution, and elimination, thus limiting the transport and absorption of drugs that may be involved in pharmacokinetic interactions [12]. In tumoral cells P-glycoprotein reduces the intracellular concentration of the drug, limiting the action of chemotherapeutics at the site of infection [12].

Pharmacokinetic interactions are mostly related to CYP450 or P-glycoprotein which influences the efficacy of the drug, regulating its distribution and bioavailability [14].

## 1.4 Micromedex Database

Micromedex is a database developed by IBM. In this database, it is possible to find information such as drug interaction with other drugs, food, or alcohol, for example.

### *1.4.1 Severity*

Drug interactions could be grouped according to their severity, that is, they are divided according to the damage that they cause to the patient. So, drug interactions could be classified in the following grades: contraindicated, major, moderate, minor, and unknown.

According to the literature and Micromedex database, a contraindicated interaction means that two or more drugs cannot be administered concurrently [15]. Major interactions are those whose adverse effects can cause permanent damage to the patient or put the patient's life at risk, requiring intervention by health professionals [11], [15]. Moderate type interactions are less severe than major types, however, can change/modify the patient's clinical condition and medical treatment is necessary to reduce exacerbations and reframe the therapeutic regimen [11], [15]. Minor interactions show mild, that is, uncomplicated clinical consequences and therefore do not require medical intervention [11], [15]. When the severity of interaction is classified as unknown, this means there is no information and research on it [15].

### *1.4.2 Grade of Evidence*

A drug interaction's degree of evidence is related to the quantity and quality of underlying documentation for the data provided, the interaction explained, and its severity. This parameter is classified according to the following characteristics: excellent, good, fair, and unknown.

In accordance with Micromedex, the grade of evidence is classified as excellent when the documentation used includes studies that clearly describe the interaction, and these studies were controlled [15]. When the degree of evidence is presented as good, the documentation doesn't represent very controlled studies, however, it strongly suggests that the interaction exists [15]. A fair grade of evidence arises when documentation is poor, however, professionals with available pharmacological evidence suspect the existence of interaction, or else when there is documentation classified as excellent for similar drugs [15]. As in gravity, classification as unknown means there is no information and research on it [15].

There are still no significant studies regarding drug interactions with oral antineoplastic, namely, interactions with opioid analgesics. So, the main objectives of this study were: (a) to identify possible drug-drug interactions between oral antineoplastic agents and opioid analgesics; (b) to assess the severity of drug-drug interactions between oral antineoplastic agents and opioid analgesics, and (c) To describe the mechanisms of interactions.

## 2 Methodology

In this project, a descriptive cross-sectional observational study was conducted related to drug interactions between oral antineoplastic and opioid analgesics. This investigation was conducted between April 2020 and June 2021.

Potential drug interactions were collected, using the Micromedex database. For this data collection, the drugs used were selected in FHNM ("Formulário Hospitalar Nacional do Medicamento") and combined one by one to find specific drug-drug interactions, their severity, and the grade of evidence. This data collection was carried out on April 23, 2020. The results were organized in an Excel file. Six drug interactions were selected to be properly explained.

## 3 Results

Following the analysis and collection of the drugs from FHNM, twenty-seven oral antineoplastic agents were selected (anastrozole, azathioprine, bicalutamide, busulfan, chlorambucil, cyclophosphamide, cyproterone, cyclosporine, etoposide, flutamide, hydroxycarbamide, idarubicin, imatinib, letrozole, lomustine, megestrol, melphalan, mercaptopurine, methotrexate, mitotane, mycophenolate mofetil, procarbazine, estramustine, tacrolimus, tamoxifen, thalidomide, and thioguanine) and seven opioid analgesics (buprenorphine, fentanyl, hydromorphone, morphine, oxycodone, tapentadol, and tramadol).

After introducing one hundred and eighty-nine pharmaceutical combinations into Micromedex database, twenty-three interactions were detected (Table 1). Subsequently, analyzing the table, it was observed that the antineoplastic drug with the highest number of potential interactions was procarbazine (seven interactions, being five major and two contraindicated). Regarding opioids, the one with the greatest number of possible interactions (six interactions, in this case, all major) was buprenorphine.

All interactions found were grouped according to severity and grade of evidence (Table 1). Of the twenty-three interactions collected, most had a higher degree of severity (twenty-one interactions), with the remainder being classified as contraindicated.

Regarding the degree of evidence, the twenty-three interactions collected are found to have three different levels of evidence (excellent, good, and fair), with most being fair, only three interactions having an excellent level of evidence, and three others being good.

**Table 1.** Severity and grade of evidence of interactions

| **Antineoplastic agent** | **Opioid analgesic** | **Severity** | **Grade of evidence** |
|---|---|---|---|
| Cyclosporine | Buprenorphine | Major | Fair |
| | Fentanyl | Major | Excellent |
| | Morphine | Major | Good |
| | Oxycodone | Major | Fair |
| | Tramadol | Major | Fair |
| Imatinib | Buprenorphine | Major | Excellent |
| | Fentanyl | Major | Fair |
| | Oxycodone | Major | Fair |
| | Tramadol | Major | Fair |
| Mitotane | Buprenorphine | Major | Fair |
| | Fentanyl | Major | Excellent |
| | Oxycodone | Major | Fair |
| | Tramadol | Major | Fair |
| Procarbazine | Buprenorphine | Major | Fair |
| | Fentanyl | Major | Fair |
| | Hydromorphone | Major | Fair |
| | Morphine | Major | Good |
| | Oxycodone | Major | Fair |
| | Tapentadol | Contraindicated | Fair |
| | Tramadol | Contraindicated | Fair |
| Tamoxifen | Buprenorphine | Major | Fair |
| Tacrolimus | Buprenorphine | Major | Fair |
| | Fentanyl | Major | Good |

# 4 Discussion

Through the results, it is possible to observe the existence of twenty-three drug interactions between oral antineoplastics and opioid analgesics. In this descriptive study, six of these interactions will be addressed. The choice of those to be described was based on criteria related to their classification as to the severity and degree of evidence indicated in Micromedex. In this case, will be addressed those whose severity is major and the degree of evidence excellent or good, since they are the most worrying and documented. To explain the mechanism of interactions, first a little bit of the pharmacokinetics of each drug will be discussed.

## 4.1 Buprenorphine-Imatinib

Buprenorphine, a partial opioid agonist of mu receptors, is used to treat pain, as well as can be used in the treatment of opioid addiction [16]. Since it is a partial agonist it can cause analgesia, sedation, and respiratory depression [4], [16]. This opioid has a large volume of distribution and is extensively bound to plasma proteins [16]. Regarding the metabolism inherent to this drug, it is highly metabolized to norbuprenorphine, an active metabolite, through the CYP3A4 isoenzyme through a reaction called N-dealkylation, which results in an inhibition of the said isoenzyme [16], [17]. Concomitant administration with other drugs known to induce or inhibit this enzyme complex may result in drug interactions that will affect its pharmacokinetics since it will decrease or enhance N-dealkylation which will result in an increase or decrease in the amount of buprenorphine circulating in the body [16].

Imatinib is an inhibitor of tyrosine kinase protein, Bcr-Abl, a fusion oncoprotein, resulting from a translocation present in chronic myeloid leukemia (CML) [18]. Protein tyrosine kinases participate in several cellular processes such as growth, differentiation, metabolism, adhesion, and apoptosis, meaning that the dysregulation of the activity of this protein is associated with several types of cancer, namely chronic myeloid leukemia and gastrointestinal stromal tumor [19]. Since Bcr-Abl was very present in CML, this protein was thought to be the target of inhibition, and imatinib is used for this purpose, which acts on the binding site of adenosine tri-phosphate by competitive inhibition, resulting in selective inhibition of proliferation and apoptosis in Bcr-Abl positive cells not affecting normal cells [19]. The imatinib is quickly absorbed after oral administration [19]. This drug is metabolized mainly in the liver by the isoenzymes CYP3A4 and CYP3A5 [18]. The metabolites of this drug undergo bile excretion [18], [20]. Imatinib metabolism can be decreased and its plasma concentrations increased when administered concomitantly with drugs that inhibit CYP3A4 or CYP3A5 [19]. On the other hand, drugs that induce these enzymes can increase metabolism and decrease exposure to imatinib, as is the case with pro-carbamazepine [19].

According to the Micromedex database, the simultaneous use of CYP3A4 inhibitors with imatinib should be carried out with caution [15]. Knowing that imatinib is a potent inhibitor of CYP3A4 and that this isoenzyme is responsible for the metabolism of buprenorphine to norbuprenorphine, it is possible to understand that there may be an increase in the

concentration of buprenorphine [18]. This increase in the concentration of buprenorphine may result in the inhibition of cardiac repolarization, the prolongation of the QT interval, reduction in heart rate, and respiratory depression which, once installed, can be difficult to reverse [16], [17]. Therefore, it is recommended to monitor the symptoms of the patient who is undergoing antineoplastic therapy together with opioids in adjuvant therapy, as well as to consider reducing the dose of buprenorphine, since in this case, it will result in a lower concentration of opioid in circulation and therefore fewer adverse effects [15].

### 4.2 Fentanyl-Mitotane

Fentanyl is a drug belonging to the group of opioid analgesics, μ-receptor agonists, which when acting on opioid receptors gives rise to analgesic and sedative effects, being used in the maintenance of cancer-associated pain [21]–[23]. In terms of metabolism, this drug is metabolized, in the first stage, by the enzyme CYP3A4 present in the liver, responsible for a first-pass process (N-dealkylation) [23]. This type of metabolism can give rise to various drug interactions when fentanyl is administered concomitantly with inducers or inhibitors of the CYP3A4 isoenzyme [23]. These interactions may result in harmful effects for the patient due to the increased time of exposure to fentanyl, which may result in respiratory depression and skeletal muscle stiffness [4], [23].

Mitotane, used in Cushing's syndrome and adrenocortical carcinoma, belongs to the group of oral antineoplastics [24]–[27]. It is considered a drug that strongly induces CYP3A4 by activating SXR (steroid and xenobiotic receptor) [25]. Due to its strong activity on this enzyme complex, mitotane should be used with great caution, since it will affect the pharmacokinetics of other drugs, even after the cessation of its administration, this means that its strong activity on CYP3A4 is prolonged for months [26].

The data provided by Micromedex indicate that the interaction mechanism between the two drugs discussed in this point is related to the isoenzyme 3A4 of the CYP450 enzyme complex [15]. Considering the strong induction of CYP3A4 by mitotane and fentanyl being an inhibitor and a substrate of this isoenzyme, it is important to highlight the existence of drug interaction when these two drugs are administered concomitantly. In their study Kroiss et al. (2011) state that when mitotane is administered with this type of drug it will have an uncontrolled effect on them that may manifest itself in an increase in plasma concentration, in this case of mitotane, once fentanyl neutralizes the inducing effect of mitotane [24]. The opposite is also likely to be the case if the CYP3A4-inducing activity of fentanyl exceeds that of mitotane, in which case an increase in the plasma concentration of mitotane will be observed [24]. A reduction in plasma fentanyl concentrations is also possible, according to Micromedex, and may lead to severe respiratory depression, so monitoring and if necessary, discontinuation of mitotane should be undertaken [15].

### 4.3 Fentanyl-Cyclosporine

As previously mentioned, fentanyl is an opioid analgesic, which is one of the opioids most often involved in drug interactions [7].

Cyclosporine used to treat autoimmune diseases and prevent transplant rejection, is a potent immunosuppressant belonging to the group of oral antineoplastic agents. It is a lipophilic molecule that, after its administration and absorption, binds to P-glycoproteins [28]. The enzyme complex in the liver composed of the cytochrome P450 isoenzyme 3A4 is the main responsible for the reactions of N-methylation that degrade most of the molecule, the rest being metabolized in the gastrointestinal tract, through enzymes and intestinal flora [28]. However, factors such as age, patient status, or concomitant medication can affect the pharmacokinetics of cyclosporine, interfering with its metabolism [28].

Cyclosporine acts as an inhibitor of CYP3A4. That being said, when administered concomitantly with fentanyl, it may result in a decrease in the metabolism of the opioid analgesic and a consequent increase in its plasma concentration, leading to an increased risk of toxicity by the opioid. However, by decreasing the metabolism of fentanyl, there is an increase in the effectiveness of this drug, consequently, reactions such as sedation and respiratory depression may also occur [7], [15]. Another problem comes from withdrawal syndrome which manifests itself after discontinuing the administration of fentanyl, which although a small dose was administered, due to cyclosporine increasing its plasma concentration. For this reason, it is necessary to monitor the patient and reduce the opioid dose administered [15].

### 4.4 Morphine-Procarbazine

Morphine is a natural alkaloid, being the most commonly used opioid to treat moderate to severe pain [29], [30]. It is a total agonist of mu-opioid receptors and its effects are mainly related to them, such as analgesia, respiratory depression, reduced intestinal motility, nausea, and sedation [29]. It also binds, albeit to a lesser extent, to the kappa and delta receptors [29]. Morphine is almost completely absorbed in the gastrointestinal tract when administered orally and quickly distributed to tissues such as kidneys, lungs, and liver that are highly fused, mostly eliminated via the liver [29]. Due to the hepatic first-pass mechanism, only 20-30% of the dosage administered orally is available [29]. The conjugation with glucuronic acid results in two metabolites: morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) [29], [30]. Absorption by intramuscular administration is fast and total [29]. However, some factors influence absorption after intramuscular administration, for instance, site of application, pH of the injection site, tissue perfusion, and lipophilicity of the drug [31]. Having a short half-life, it should be administered every 4 hours [31].

When administered orally in repeated doses, morphine becomes very effective primarily as a result of the production of the active metabolite M6G during the first passage through the liver and being accumulated with successive administrations [31]. M6G binds to mu receptors and has greater analgesic potency than morphine [31]. Patients with impaired kidney function are more sensitive to morphine and may experience severe respiratory

depression [31]. Morphine blocks the transmission of nociceptive signals, activates signaling by pain-modulating neurons to the spinal cord, and inhibits the transmission of primary afferent nociceptors [30]. M3G has no analgesic activity and has a low affinity for opioid receptors [30].

Procarbazine, a monoamine oxidase inhibitor (IMAO), has been used to treat Hodgkin's disease and brain tumors [32]. This active principle is a pro-drug whose transformation into azo-procarbazine is necessary to exert its action, and this transformation may occur in the liver or kidneys, through a reaction with molecular oxygen [33]. This transformation occurs very quickly when this drug is administered orally, having been reintroduced in the BEACOPP therapeutic regimen, composed by the association of this drug with bleomycin, etoposide, doxorubicin, vincristine, and prednisone [32].

Considering that morphine has depressive effects, essentially respiratory, and procarbazine is a MAO inhibitor and consequently a central nervous system depressant, the concomitant administration of these two drugs may be harmful to the patient's well-being, since it could result in the potentiation of the effects of morphine, resulting in respiratory depression, coma, deep sedation or hypotension, a result of decreased CYP450 activity by procarbazine [33], [34]. To avoid this situation, because the combination of these two drugs increases the risk of mortality, when compared to the isolated administration of each one, it is necessary to proceed with a 14-day spacing between taking each of them [34].

### 4.5 Morphine-Cyclosporine

As mentioned before, morphine is an alkaloid used to treat severe to moderated pain and cyclosporine is an immunosuppressant, used in oral antineoplastic therapy.

In accordance with Micromedex, concomitant use of morphine and cyclosporine can result in increased morphine exposure [15].

Cyclosporine is a P-glycoprotein inhibitor and inhibits the activity of the human blood-brain barrier P-glycoprotein [35]. By inhibiting P-glycoprotein, cyclosporine is blocking the entry of morphine into the brain, which reduces its action [35]. It can also lead to accumulation in the blood flow [35]. Also by inhibiting CYP3A4, cyclosporine inhibits the metabolization of morphine, causing an increase in adverse effects of morphine, such as miosis and respiratory depression [35]. Morphine at high concentrations can also cause anxiety, aphasia, and amnesia [15].

### 4.6 Fentanyl-Tacrolimus

As previously mentioned, fentanyl is a drug belonging to the pharmacotherapeutic group of opioid analgesics, used in the treatment of cancer-derived pain, whose metabolism is made by the isozyme CYP3A4 through a reaction called N-dealkylation [4], [21]–[23].

The tacrolimus is an antineoplastic agent with immunosuppressant action, used in organ transplantation for the prevention of rejection and the treatment of autoimmune diseases [36].

It can be found in different presentations, from injectables for intravenous administration to capsules for oral administration [36].

Considering its narrow therapeutic range, this drug must be carefully controlled when administered to avoid possible complications for patients, which also applies to potential drug interactions, since a blockage of its metabolism can be very harmful [36]. The metabolism of tacrolimus involves the liver isoenzymes, 3A4 and 3A5, of the CYP450 enzyme complex [36]. This process that occurs by 6b-hydroxylation gives rise to the active metabolite of tacrolimus called mono-demethylated [36].

The concomitant use of drugs also metabolized by these enzymes may result in a decrease in the effects of tacrolimus, which may result in transplant rejection in the patient [36]. After its metabolism, most of the elimination of tacrolimus occurs via bile or feces [36].

The treatment with oral antineoplastic agents, in this case, tacrolimus, has several side effects, one of which is oral and nasopharyngeal mucositis, which is the source of the pain associated with cancer treatment [37]. Bearing in mind that fentanyl has fewer adverse effects than drugs belonging to the same group, it has become the first choice in the maintenance of cancer-associated pain, therefore the concomitant administration of fentanyl and tacrolimus has become a recurrent practice in combating pain derived from the adverse effects of the antineoplastic [37].

As previously mentioned, both fentanyl and tacrolimus have a metabolism that passes through the P450 enzyme complex, more specifically through the 3A4 isoenzyme. When these two drugs are administered concomitantly, they will compete for this isoenzyme to be metabolized, and the one with the greatest affinity will be metabolized first. Since these two drugs are classified by the FDA (Food and Drug Administration) as having a narrow therapeutic window, this problem becomes important due to the effects that this interaction may have [37]. In a study by Kitazawa et al (2017) that aimed to determine the existence of drug interaction between fentanyl and tacrolimus, it was shown that when administered concomitantly there is a 46,9% decrease in tacrolimus clearance, which means the increase in blood concentration with the possibility of reaching toxic levels [37].

The biggest limitation of the present study was finding documentation related to the studied interactions, which proves the lack of information existent about this theme and highlights the existing need for more research.

## 5 Conclusion

Monitoring of possible drug-drug interactions in cancer patients is becoming more and more pertinent with the increasing use of oral antineoplastic agents. Cancer patients are usually polymedicated due to comorbidities. It would be important to raise awareness on the part of the prescribing doctors so that they were more careful when prescribing opioid analgesics to patients undergoing cancer treatment, often having to analyze the risk-benefit of the treatment.

As demonstrated in this study, most of the interactions studied are related to cytochrome P450 and its enzymes. It is possible to conclude that all interactions described are classified as pharmacokinetic, related to the metabolism and distribution of the drugs involved, except for the interaction between morphine and procarbazine which represents a synergism, therefore it is pharmacodynamic.

Since the interactions found were in the highest classification levels in terms of severity allow to conclude about the concern regarding the occurrence of these interactions and the importance of greater pharmacovigilance.

In this study, the proposed objectives were achieved, with twenty-three interactions found.

In future perspectives, it would be important to investigate the remaining drug interactions taken from the Micromedex database and quantify the frequency in which they occur.

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