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Oral Chemotherapy Interactions

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INTRODUCTION

Oral chemotherapy is the most cost-effective route of administration, as well as the most accepted by both patients and physicians, however occasional pharmacological and dietary interactions causes complications in the treatment of the oncological patient.

Lifestyle and diet can have a significant impact on chemotherapy, as well as over-the-counter drugs, homeopathic, natural food and supplements. This interaction can vary from mild to severe effects; either by inhibiting or potentiating the effect of chemotherapy. While the context of this article is to address the interactions that are undesirable, it should be emphasized that not all interactions are harmful, we can take advantage of their synergism or antagonism in a therapeutic way. –

Since 1998 the FDA (American Food and Drugs Administration) has approved more than 30 oral chemotherapeutics, from the first as mercaptopurine and chlorambucil by the year 1950 to those of the latest generation with new specific molecular targets in different stages of carcinogenesis. (1,2,5) As a guide for drug developers, the FDA has created a web portal for the understanding of the elaboration of drug interaction studies and their respective labeling, as well as recognized virtual tools to facilitate doctors the review of harmful drug interactions in the daily practice.
The main objective of the following review is to provide a color warning signage table between oral chemotherapeutics and other medications as well as everyday foods.

METHODS

A bibliographic search was conducted with two readers in meta search engines such as Pubmed and Tripdatabase as well as in the developer of clinical information solutions Lexicomp and "Drugs Interactions", filtering articles that relate interactions between oral chemotherapeutic drugs, commonly used drugs and specialty drugs approved by the FDA; as well as daily consumption food. We obtained 45 articles from the year 1997 to the year 2017.

Pharmacological interactions with oral chemotherapeutics were defined as inducers or inhibitors if the interaction increases or decreases the plasma concentration, respectively, of the chemotherapeutic drug that was metabolized by a CYP450 enzyme.

Information was collected on the fasting or food intake with oral chemotherapeutic agents, as well as their interaction with foods rich in phytoestrogens, or fruits.

The pharmacological and food interactions of the identified drugs was tabulated, using a traffic light as a warning guide when using the named chemotherapeutic agent. (Annex 1)

Vidal's Interactions médicamenteuses classifies the severity of medicine interactions in four levels (contraindicated, avoid, precaution, and "take into account"). Drug Interaction Facts classifies the severity of an interaction into three categories (major, moderate, and minor). Micromedex Drug–Reax System classifies the severity of an interaction in three categories (major, moderate, and minor). These classification systems determine the degree or the severity of the result of interaction depending on whether the reaction puts the life in danger or if it generates clinical effects that can be simply managed. The NHS classify the drug prescription into four colors: Red, Amber, Green, Grey, depending on the level of care that should prescribe, being red: prescribed by specialist, Amber: prescribed initially by a specialist and continued prescription in primary level, Green: Prescribed initially by primary care, Grey: Item withdrawn from market/discontinued. These classification use these colors because of the common knowledge of the traffic light colors, relating the colors with better of worst outcomes (29, 31)

Taking into account these classifications we classified the interactions in three groups, relating the colors with the universal traffic lights. Being green: no interactions reported, should be administer freely with clinical indications. No monitoring interactions required. Yellow: no important clinical interactions found or clinical manifestations that can be easily managed as epigastralgia or decreased absorption or effect of the oral chemotherapy, should be administer with medical criteria measuring the benefits versus the risks taking. Minimal monitoring required and Red: life threatening clinical manifestations derived from interaction of oral chemotherapy and the agent described, this should be known or proved so the clinician should avoid prescribing interacting agents of this table and if two agents that interact are selected continued monitoring is required.

RESULTS

We identified 56 drugs that include oral chemotherapeutics, hormonal drugs, tyrosine kinase inhibitors, foods and herbal medicines, determining the main interactions that occur at the cytochrome CYP 450 level, represented in an aid traffic light, classifying the administration recommendation: red do not administer by having strong interaction evidence, yellow administer with caution for having moderate interaction evidence, green can be administered freely with no interaction described.

DISCUSSION

Oncologic patients have a high risk of presenting drug interactions. There are several predisposing factors such as the use of a significant number of drugs involved in the treatment of oncological pathology such as the cytostatics, hormones, antiemetics, analgesics, antibiotics, antifungals. The frequent use of alternative medicines without the control or knowledge of the physician. The co-morbidities that are usually present in

oncological patients, polimedicated by their secondary diagnoses. The change in pharmacokinetics due to the organic deterioration of the patients that accompany their basic pathology or aging. The characteristics of many chemotherapeutics such as the narrow therapeutic index and the steep slope of the dose-response curve. (1)

It is important to recognize the pharmacological interaction before initiating the oncological treatment since many of the symptoms are not recognized when they are masked by some symptoms of the underlying pathology or are assumed as toxicity attributed to the use of chemotherapy.

The most commonly used administration route for antineoplastic treatments is the parenteral route, although the oral route is preferred in specific first-line treatments such as metastatic colorectal cancer with capecitabine. The new antineoplastics drugs with mechanisms of action based on blocking new therapeutic targets are of oral administration. The FDA recommends carrying out bioavailability studies for the new oral drugs to demonstrate that they are bioequivalent in both administration situations, both in fasting and with food. (1)

From 2002 to 2006, publications on drug-food interactions represented around 10% of all publications in Pubmed, with only 1% having a clinical trial methodology. (1)

In the table developed in this article you can see the main interactions with foods described in the literature reviewed, as well as in a fasting situation inferring a change in the pharmacokinetics of the chemotherapeutic used. It can be observed that the food that has more red tags is the grapefruit juice, described in many references as a potent inhibitor of the intestinal activity of CYP3A4. It can also be observed that coffee has a significant number of pharmacological interactions described from moderate to severe, from red to yellow tag. (6, 15)

Lewis et al. (6) describe the interaction of oral chemotherapeutics with foods with high fat content affecting both the absorption and distribution of the drug; they describe how a low fat intake increases the AUC of Lapatinib by 2.67 times while a high fat breakfast increases its AUC by 4.25 times, these large increases in bioavailability and absolute variability support the recommendation of fasting intake. However, in a letter to the editor published by Tannock (7) reports inconsistencies in the statistical analysis and a possible conflict of interest on the part of the authors.

Epigastralgia is a common symptom in oncological patients undergoing treatment, which is why proton pump inhibitors are commonly used. Koch et al. (8) in his clinical trial he describes that the solubility of Lapatinib is reduced with a gastric pH> 4, concluding that increased gastric pH decreases the bioavailability of this drug, so we classify with yellow flag for proton pump inhibitors with Lapatinib.

In the study of Egorin et al. (9), they demonstrate that Omeprazole does not intervene in the bioavailability of Imatinib despite altering the gastric pH, however it describes the alteration of the bioavailability of Dasatinib with the concomitant administration with omeprazole. Yin et al. (12) describes the pH-dependent solubility of Nilotinib, so in the first Imatinib scenario it is cataloged as a green flag and following scenarios with Dasatinib and Nilotinib with yellow flags.

Ranchon et al. (10) and Bazabeh et al. (11) in their reviews of adverse events reported and published by the FDA, specify how methotrexate clearance decreases with the concomitant administration of proton pump inhibitors, increasing the possible toxicity of methotrexate, so this interaction is cataloged as a red flag. Therefore, the use of H2 antagonists is recommended for concomitant use with oral chemotherapeutics.

Taking into account that an oncological diagnosis increases the likelihood of thrombosis, the use of oral anticoagulants is not recommended during chemotherapy treatment, especially warfarin, due to the alteration in hepatic metabolism generated by several chemotherapeutic agents such as capecitabine, gemcitabine and protein binding that present others such as erlotinib, both situations causing an increase in INR with considerable risk of bleeding, which is why multiple international guidelines recommend against the routine administration of oral anticoagulants during the use of oral or intravenous chemotherapy, so they are cataloged with a red flag. (13 -17)

Oncological patients often use alternative or complementary medicine based on biologically active substances such as plants, foods, vitamins, etc. The type, amount and frequency of the ingested plant will determine the type of interaction observed, although there are not enough studies to determine the amount and frequency necessary to intervene in the pharmacokinetics or pharmacodynamics of the oral chemotherapeutic agent. Alissa et al. (8) describes how certain medicinal herbs contain phytoestrogens inhibiting the effect of Tamoxifen, among plants that contain phytoestrogens are: black cohosh, oats, soybeans, sunflower seeds, etc. So we categorizes with red flag, especially if there is a diagnosis of hormone-dependent breast cancer.

Different ways of kidney injury can be caused by medicinal plants with the concomitant use of certain oral chemotherapeutics, especially Chinese medicinal plants that often contain ephedrine, oxalates, opioids with diuretic or anuric effects, causing damage in the renal tubules. So it is placed with a red flag, contraindicating the use of medicinal plants during treatment with oral chemotherapeutics. (19, 20)

Patients with cancer have a high consumption of nutritional supplements due to the weight reduction that they present as a natural disease process, there are no studies that describe interactions of nutritional supplements with oncological treatment, however its use is recommended in situations of cachexia. (21, 22)

A potent inducer of the CYP3A4 is Saint John's Wort also known as Hypericum perforatum, historically used for magic potions during the Middle Ages and then used to treat depression, anxiety and premenstrual síndrome. It contains the anthracene derivatives hypericin and pseudohypericin, the flavonoids hyperozide, quercitrin and isoquercitrin, xanthones, hyperforin, volatile oil, catechin tannins and caffeic acid derivatives. Some of wich contributes to their effects in central nervous system. Their activity within CYP3A4 decreased exposure with the active metabolite of irinotecan and decrease the anti neoplastic activity. It also decrease the elimination of imatinib by 43%. Co-administration of Saint john's Wort with oral chemotherapeutics can decrease plasma concentrations of the chemo active compounds specifically with medications that are substrates of P-gp and CYP3A substrates, this implies that chemothery will have no effect on the disease but it will not produce a fatal adverse effect, considering this facts its cathegorized as yellow flag. (23, 24)

Garlic contains Alliin/allicin, fructosan, sponin and it's normally used as an Antilipidaemic, antihypertensive, antithrombotic, anti-infective, anticarcinogenic it induces the CYP2E1 activity, increasing the risk of bleeding in patients using anticoagulants or in patients with bonemarrow suppression. It reduces the activity of etoposide, paclitaxel, vinblastine and vincristine. Because it doesn't increment the toxicities of the oral chemotherapies we catalogued as a yellow flag considering in patients with bone marrow suppression as a red flag. (27, 28)

In this review, we describe and tabulate the most discussed pharmacological interactions with oral chemotherapeutics and over-the-counter medications as well as foods or medicinal herbs, creating a guide semaphore for health professionals. An adequate communication with the patient is recommended so that the medication or alternative medicine that the patient is using are informed to the doctor avoiding an undesirable pharmacological interaction. The limitation of this review is that the exact molecular mechanisms of drug interactions of each selected element is not

described.

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