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Insights about drug interactions used in lymphoma treatments and in experimental COVID-19 therapy

Considerações sobre interações entre medicamentos usados no tratamento de linfomas e na terapia experimental da COVID-19

Consideraciones sobre las interacciones entre los fármacos utilizados en el tratamiento de linfomas y en la terapia experimental de COVID-19

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Abstract
Lymphomas are neoplasms characterized by an immunocompromised tumor environment that induces inflammatory processes whose defense cells production can be further affected by chemotherapy. These details lead to the supposition that individuals with these cancers have more severe clinical complications when contaminated by SARS-CoV-2, which makes it necessary to pay attention to the correct therapeutic management. This study summarizes the drugs used in the treatment of lymphomas and in the experimental therapy of COVID-19, and discusses the possible interactions expected between the drugs used in both illnesses. Most drug-drug interaction occur through changes in the cytochrome P450 enzyme system metabolism or the P glycoprotein efflux transporter (gp-P). Depending of combinations, there may be an increase or decrease in the concentration of the drug and, consequently, an increase in toxicity or a decrease in efficacy, which means that pharmacokinetics should be strongly considered to promote drug safety and better management patients with COVID-19 and lymphomas.
Keywords: SARS-CoV-2; Hodgkin; non-Hodgkin; Drug-drug interaction; Cytochrome P450 enzyme system.

Resumo
Os linfomas são neoplasias caracterizadas por um ambiente tumoral imunocomprometido que induz processos inflamatórios cuja produção de células de defesa pode ser posteriormente afetada pela quimioterapia. Esses detalhes levam a supor que indivíduos com esses cânceres apresentam complicações clínicas mais graves quando contaminados pelo SARS-CoV-2, o que torna necessário a atenção para o correto manejo terapêutico. Assim, este estudo resume os medicamentos usados no tratamento dos linfomas e na terapia experimental da COVID-19, e discute as possíveis interações esperadas entre os medicamentos. A maioria das interações medicamentosas ocorre por meio de alterações no metabolismo do sistema enzimático do citocromo P450 ou no transportador de efluxo da glicoproteína P (gp-P). Dependendo das combinações, pode haver aumento ou diminuição da concentração do medicamento e, consequentemente, aumento da toxicidade ou diminuição da eficácia, o que significa que a farmacocinética deve ser fortemente considerada para promover a segurança do medicamento e melhor manejo de pacientes com COVID- 19 e linfomas.
Palavras-chave: SARS-CoV-2; Hodgkin; não-Hodgkin; Interação droga-droga; Sistema enzimático do citocromo P450.

Resumen
Los linfomas son neoplasias caracterizadas por un entorno tumoral inmunodeprimido que induce procesos inflamatorios cuya producción de células de defensa puede verse posteriormente afectada por la quimioterapia. Estos detalles llevan a suponer que los individuos con estos cánceres tienen complicaciones clínicas más graves cuando son contaminados por SARS-CoV-2, lo que hace necesario prestar atención al correcto manejo terapéutico. Por lo tanto,

este estudio resume los medicamentos utilizados en el tratamiento de linfomas y en la terapia experimental de COVID-19, y analiza las posibles interacciones esperadas entre los medicamentos. La mayoría de las interacciones farmacológicas se producen a través de cambios en el metabolismo del sistema enzimático del citocromo P450 o en el transportador de eflujo de la glicoproteína P (gp-P). Dependiendo de las combinaciones, puede haber un aumento o disminución de la concentración del fármaco y, en consecuencia, un aumento de la toxicidad o una disminución de la eficacia, por lo que se debe considerar fuertemente la farmacocinética para promover la seguridad del fármaco y un mejor manejo de pacientes con COVID-19 y linfomas.
Palabras clave: SARS-CoV-2; Hodgkin; no Hodgkin; Interacción fármaco-fármaco; Sistema enzimático del citocromo P450.

1. Introduction

On March 11, 2020, Coronavirus Disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO). It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has high transmissibility and affinity for lung cells, and is disseminated through close contact and droplets (Chu, et al., 2020). Respiratory symptoms of COVID-19 can cause alveolar damage and/or the acute respiratory distress syndrome (ARDS) (Huang, et al., 2020; Xu, et al., 2020), and comorbidities such as hypertension, obesity, diabetes, heart disease and cancer can get worsen the clinical picture and to reduce patient survival (Richardson, et al., 2020; Wang, et al., 2020).

Cancer is the disordered division of cells into subjacents tissues and organs (INCA, 2020), being called lymphoma when it occurs in lymphocytes. Hodgkin or non-Hodgkin are the types and both compromises the immune function. The most appropriate treatment depends of lymphoma type and stage, which normally limit the bone marrow performance and weaken the patient, increasing the risk of acquired infections as COVID-19 (He, et al., 2020).

The exceptional context of the COVID-19 pandemic has brought profound changes in the fight against cancer. The oncology clinical pharmacy now has to take new risks, with all the concerns that this entails, and respond in an emergency with new knowledge that is already opening up opportunities for an adequate treatment management for cancer patients (Slimano, et al., 2020). With the ongoing pandemic and the risk of acquisition by cancer patients undergoing treatment, oncologists should be aware about the effects of drugs used in virus experimental therapy and their possible interactions with antineoplastic agents used commonly (Di Lorenzo, et al., 2020), because one of the most important problems in pharmacotherapy is drug interaction (DDI), which can significantly increase the adverse effects of the drug (Rezae, et al., 2020).

So, the situation requires an analysis about drug interventions, since understanding them makes more effective monitoring necessary to identify the best interventions for treatment decisions and encourage studies in the area. Thus, this study summarizes the drugs used in the treatment of these lymphomas and in the experimental therapy of COVID-19, and discusses the possible interactions expected between the drugs used in both situations, highlighting current uncertainties for projection of clinical practice and future researches.

2. Methodology

The present study has descriptive character, configuring in a narrative review of literature, according to Ferrari (2015), constructed from the scientific production about interactions between drugs. A systematic research was carried out using *Health Sciences Descriptors* (DeCS), from Biblioteca Virtual em Saúde, and *Boolean Search* in the databases Medical Literature Analysis and Retrieval System Online (Medline), ScienceDirect, Scopus and Scientific Electronic Library Online (SciELO) and their corresponding acronyms when applicable: “COVID-19”; “SARS-CoV-2 infection”; “Drug interactions”; “Hodgkin and non-Hodgkin lymphomas”; as well as *Phrase Searching*: “drugs used in therapy against Hodgkin and non-Hodgkin lymphomas”; “experimental therapy against COVID-19”; “drug-drug interactions”; “cytochrome P450 enzyme system”, in English, Spanish and Portuguese languages.

To refinement of the material, the publications were included in the form of scientific articles, research, review, or book chapters, without restriction of the publication year, but that supported the discussion of the themes. The results include a description of the antineoplastics used in the treatment of these malignancies and in the experimental therapy of COVID-19, and the interactions between the drugs that can occur when co-administration. References for all eligible studies have been revised to identify other potentially eligible studies.

3. Results and Discussion

3.1 Therapeutic agents for COVID-19

Since it was declared a pandemic, the search for antiviral drugs to fight COVID-19 has been a global concern due to the seriousness of specific cases, which can lead to the patient's death. Although preventive vaccines are already available, the needed urgency to identify treatments for COVID-19 go on and has required in-depth investigations of therapeutic agents. Certain candidates are being reused for having confirmed *in vitro* activity against other respiratory viruses and thus administered to COVID-19 patients for analysis of their effectiveness in isolation or combination (Ko, et al., 2018; Ahn, et al., 2020).

According to the pathophysiology of the disease, several drugs were evaluated in different clinical conditions of the disease. Some medicines considered for therapy anti-SARS-CoV-2 (Ayerd, et al., 2020; Cao, et al., 2020; Chaccou, et al., 2021; Chen, et al., 2020; Dabous, et al., 2021; FDA; Grein, et al., 2020; Meriglier, et al., 2020; Nojomi, et al., 2020; Recovery Collaborative Group, 2020; Toniat, et al., 2020) identified in this review are shown in Table 1**.**

Table 1. Tested treatments for Covid-19.

Antiviral drugs	Description / Effect	Reference
Lopinavir	Antiretrovirals used in combination to treat HIV infections. Lopinavir is a viral protease inhibitor whose action is enhanced by ritonavir, because it has low oral bioavailability and extensive metabolism in the liver.	(Page & Taylor, 2018; Hull & Montaner, 2011)
Ritonavir		
Tenofovir disoproxil fumarate (TDF)	Acyclic nucleotide analogue of adenosine approved for treatment against HIV in combination with other antivirals. After absorption, it is converted to tenofovir, an HIV-1 reverse transcriptase and viral polymerases inhibitors by direct binding and after incorporation into DNA.	(Wassner, et al., 2020)
Darunavir	HIV protease inhibitor. It is used in combination with ritonavir.	(Back, et al., 2008)
Arbidol (Umiferovir)	Indole-derived antiviral administered in Russia and China for prophylaxis and treatment against human respiratory viruses. It inhibits hemagglutinin and blocks the influenza virus fusion with the host cell, induces the immune system to produce interferon against viral replication, and improve the function of phagocytic macrophages and activate NK cells.	(Blaising, et al., 2014)
Remdesivir	It is a monophosphoramidate prodrug of an adenosine analog with antiviral activity demonstrated against Ebola, Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus, Nipah and Hendra. It acts as RNA-dependent RNA polymerase inhibitor.	(Sheahan, et al., 2020)
Chloroquine (CQ)	Synthetic derivative of aminoquinolone obtained from chinchona bark. It was developed for the malaria treatment and its applications have also been proposed for SARS infections. It helps to increase the endosomal pH necessary for virus / cell fusion, and interferes with the glycosylation of surface receptors, such as ACE2 in Vero cells.	(Liu, et al., 2020)
Hydroxychloroquine (HCQ)	It is a 4-aminoquinoline derived from QC and is less toxic to the body. It has an action similar to QC, but with a greater safety profile.	(Schrezenmeier & Dörner, 2020)

Favipiravir (T-705)	Antiviral approved in Japan to treat influenza virus infections. It is believed that it integrates with viral RNA or conserved polymerase domains, a condition that prevents the incorporation of nucleotides necessary for the viral genetic material duplication and transcription.	(Furuta, et al., 2013)
Ivermectin	Macrocyclic lactone with antiparasitic activity. It acts as a substrate for the CYP3A4 isoenzyme, but it is assumed that the glycoprotein P is the main target of this drug, guaranteeing its antiviral potential.	(Jafari, et al., 2020)
Azithromycin	Semi-synthetic macrolide antibiotic derived from erythromycin. Macrolides are anti-inflammatory drugs whose immunomodulatory effects include reduced neutrophil chemotaxis into the lungs, reduced mucus secretion and the formation of reactive oxygen species.	(McMullan & Mostaghim, 2020)
Convalescent plasma	Passive immunotherapy based on plasma transfusion from donors who have recovered from serious infections, because it contains immune memory elements. It can eradicate the pathogen through activation of the complement system, antibody-dependent cellular cytotoxicity and / or phagocytosis and it has been used in outbreaks of SARS, avian influenza A (H5N1), influenza A (H1N1), MERS and Ebola virus.	(Brown & McCullough, 2020)
Interferons (IFN)	Group of cytokines produced by viral stimulation of toll-like receptors. IFNs can reduce viral replication, inhibiting the formation or accelerating the decay of capsids, or indirectly, stimulating cytotoxic T lymphocytes.	(Zhang & Gui, 2012)
Tocilizumabe (TCZ)	Humanized monoclonal immunoglobulin G1 anti-IL-6 receptor that suppresses inflammation by blocking the binding with IL-6R to block downstream signal translation.	(Kishida, et al., 2011)

Source: Authors.

Until then, no documented specific anti-SARSCoV-2 drug regimen to treat critically ill patients has been approved. Drugs fail in the clinic for two main reasons: (i) They may not work and / or (ii) they are not safe, needing to be tested and validated through *in vitro* and *in vivo* assays. However, the reported evidence so far in randomized studies are still insufficient, the restrictions verified may be due to the urgency because of the disease severity and, perhaps, the medical resources scarcity, impeding the efficient projection of studies (Hughes, et al., 2020).

3.2 Therapeutic agents for lymphoma

Chemotherapy is one of the main treatments for cancer and involves the use of drugs to destroy tumor cells. Some drugs are of natural origin, others are synthetic derivatives and are available on the market, comprising different treatment protocols that involve the combination of different compositions, doses and periods, depending on the specificity of the cases. Table 2 lists the main drugs used to treat Hodgkin and non-Hodgkin lymphomas.

Table 2. Medicines for the treatment of Hodgkin and non-Hodgkin lymphomas.

Drugs	Effects on tumor cells	Chemical nature / Origin	Reference
Vincristine	Interrupt the mitotic spindle in the S and M phases, interfere with the metabolism of amino acids, nucleic acids, cyclic AMP, glutathione, calmodulin-dependent calcium transport, mitochondrial respiration and lipid biosynthesis	Alkaloids isolated from *Catharanthus roseus* and *Vinca rosea* Linn.	(PubChem, 2004; Ramezani, et al., 2018)
Vinblastine			
Procarbazine	Inhibits methionine transmethylation in transfer RNA and causes oxidative DNA damage	Benzamide derived from methylhydrazine	(PubChem, 2004)
Prednisone	Binds to nuclear receptors to alter gene expression; promotes apoptosis.	Glucocorticoids	(PubChem, 2004; Lin & Wang, 2016)
Dexamethasone	Promotes apoptosis.		
Doxorubicin	Interleaves in DNA, inhibits topoisomerase II, promotes the production of oxygen species (ROS) and apoptosis.	Anthracycline antibiotic obtained from bacteria *Streptomyces peucetius* var. caesius	(Malla, et al., 2017)
Bleomycin	Promotes the increase of ROS, the suppression of antioxidant enzymes, the activation of growth factors, affects the expression of metalloproteinases and inhibits cellular proteinases	Glycopeptide antibiotic obtained from *Streptomyces verticillus*	(Umezawa, 2018)
Dacarbazine	Inhibits RNA and protein synthesis, blocks cell cycle and promotes apoptosis	Triazene	(Vardanyan & Hruby, 2006)
Etoposid	It exerts cytotoxicity in the S and G2 phases, promotes DNA strand breaking and apoptosis, inhibits topoisomerase II.	Semi-synthetic podophyllotoxin derived from the root of *Podophyllum peltatum*	(Conde, et al., 2017)
Mechlorethamine	creates covalent cross-links between DNA and intra-strands, inhibits DNA and RNA synthesis.	Nitrogen mustards - Synthetic alkylators	(Giuliani, 1997; Ekeleme-Egedigwe, et al., 2019; Chabner & Longo, 2011)
Cyclophosphamide	Interferes with DNA replication and RNA synthesis		
Bendamustine	Promotes intrinsic apoptosis and disrupts important genes in regulating mitotic checkpoint		
Cisplatin	Causes cellular oxidative stress, inhibits pre-mRNA splicing, promotes actin cytoskeleton disconnection, apoptosis and cell senescence	Contain platinum metallic ion	(Woods & Turchi, 2013; Fuchs, 2008)
Carboplatin			
Cytarabine	Inhibits DNA synthesis and repair	Deoxycytidine analog. It contains arabinose in its structure	(Sessa, et al., 2012)
Rituximab	Cytotoxicity in CD20-positive malignant B cells; apoptosis; sensitizes tumor cells to the effects of conventional chemotherapeutic drugs	Mouse / human chimeric IgG1-κ monoclonal antibody	(Wang & Weiner, 2008; Chabner & Longo, 2011)

Source: Authors.

3.3 Mechanisms of pharmacological interaction

Lymphoma patients are prone to polypharmacy, which already increases the risks of drug-related problems, as well as adverse events and drug interactions, although clinical studies of treatment have already been retrieved and the knowledge regarding them to take new procedures clarified. However, when talking about patients with lymphomas and COVID-19, the situation requires even more attention.

The management of cancer patients who are also affected by COVID-19 represents an additional challenge that must guarantee active treatments as well as palliative care (Lambertini, et al., 2020). When it comes to drugs, pharmacokinetics should be strongly considered, especially when referring to critical illnesses (El-Ghiaty, et al., 2020), as there is a possibility of increased toxicity or decreased efficacy of co- administered as a result of drug-drug interactions (DDI) should be evaluated (Olin, et al., 2019).

Table 3 highlights the main pharmacological interactions of experimental therapies against Covid-19 with standard antineoplastic agents for the treatment of Hodgkin and non-Hodgkin lymphomas. We did not find a high rate of interactions due to the lack of studies, in general, the most frequent DDIs are reported with ivermectin and vincristine and vinblastine.

Table 3. Pharmacological interactions between drugs for Covid-19 and antineoplastic agents for Hodgkin and non-Hodgkin lymphoma.

Drug for treatment		Interaction mechanisms	Reference
COVID-19	**Hodgkin and non-Hodgkin Lymphomas**		
Ivermectin	Vinblastine	Vinblastine increases ivermectin concentration by inhibiting p-glycoprotein	(Zhou, 2008)
Ivermectina	Dexamethasone	Ivermectin reduces the concentration dexamethasone by inducing p-glycoprotein	(Kim, 2002)
Ivermectina	Cisplatin	Ivermectin reduces cisplatin concentration by inducing p-glycoprotein	(Zhou, 2008)
Lopinavir/Ritonavir	Vinblastine	Lopinavir / Ritonavir increases the vinblastine concentration by inhibiting CYP3A4	(Makinson, 2007)
Ritonavir	Vinblastine	Ritonavir increases the vinblastine concentration by inhibiting CYP3A4	(Dömling & Gao, 2020)
Tocilizumabe	Vinblastine	Tocilizumab increases vinblastine concentration by inhibiting CYP3A4	(Zhou & Shu-Feng, 2008)
Ritonavir	Vincristine	Ritonavir increases vincristine concentration by inhibiting CYP3A4	(Cheung, 2010)
Tocilizumabe	Vincristine	Tocilizumab increases vincristine concentration by inhibiting CYP3A4	(Zhou & Shu-Feng, 2008)
Ritonavir	Prednisone	Ritonavir increases prednisone by inhibiting CYP3A4	(Flepisi, et al., 2014)
Lopinavir/Ritonavir	Prednisone	Lopinavir / Ritonavir increases the prednisone concentration by inhibiting CYP3A4	(Flepisi, et al., 2014)
Lopinavir	Cyclophosphamide	Lopinavir increases the cyclophosphamide concentration by inhibiting CYP2C8	(Backman et al., 2016)
Ritonavir	Cyclophosphamide	Ritonavir increases the cyclophosphamide concentration by inhibiting CYP2C8	(Backman, et al., 2016)
Ritonavir	Etoposide	Ritonavir increases etoposide concentration by inhibiting p-glycoprotein	(Zhou, 2008)
Chloquine	etoposide	Increased etoposide Toxicity in tumor	(Srivastava & Lee, 2015)
Chloquine	cisplatin	Increases cellular sensitivity to cisplatin	(Qu, et al., 2017)
Chloquine	Cyclophosphamide	Increased Cyclophosphamide effect	(Gaudin, et al., 1971)
Hydroxychloroquine	Azithromycin	Increased effect of Hydroxychloroquine	(Gautret, et al., 2020)
Tocilizumab	Dexamethasone	Dexamethasone reduces the IL-6 synthesis by tocilizumab	(Leszczynska, et al., 2019)
Tocilizumab	Cisplatin	Increased cisplatin cytotoxic effect	(Alraouji, et al., 2020)

Source: Authors.

The projected scarcity of health care resources, as well as the anticipated increased risk of cancer treatment during this pandemic period, makes difficult decisions about how and when to provide cancer treatment need to be made (Ueda et al., 2020). Although protocols for the treatment of cancer involve well-established combinations of different drugs, little is known about their interactions with those being tested for COVID-19, as data on the combined use of the drugs are still very limited.

Cancer patients probably would have received antineoplastic drugs days before the diagnosis of COVID-19, needing supplementary protection during the treatment of the infection, constituting a double iatrogenic issue: anticipating the immunosuppressive impact of certain anti-COVID-19 drugs at risk of worsening symptoms; and manage the drug interaction between the anti-COVID-19 drug and the antineoplastic drugs. This double risk must be considered in the infection of low symptom concomitant with progressive cancer, where the treatment of this can be continued or adapted (Slimano, et al., 2020).

Drug-Drug interactions (DDIs) generally occur when one drug is administered before the 4-5 half-life of another (Ito et al., 2011). DDIs tend to promote reduced and / or adverse action, improved therapeutic effect or a new clinical manifestation development, however, it is common for the drugs involved to act in the same physiological pathway, which may influence the absorption, distribution, metabolism and excretion of medications (Blower, et al., 2002).

Many DDIs result from a change in the cytochrome P450 enzyme system (CYP450) metabolism, composed of more than 50 isoenzymes involved in the detoxification of xenobiotics, metabolism and cellular homeostasis. So the induction or inhibition of its enzymes are important mechanisms underlying DDIs (Manikandan & Nagini, 2018). Each CYP isoform has a specific substrate, and drugs can to stimulate or inhibit its own isoenzyme. In this scenario, an inhibitory drug tends to reduce the metabolism of substrates in the metabolic pathway, favoring the adverse effects manifestation. Another DDI site occurs through drug transporters, such as the P glycoprotein efflux transporter (gp-P), responsible for drugs transporting and disposing (Martin & Fay, 2001).

Combinations of antiretroviral therapies are at risk of DDIs with antineoplastic agents (Olin et al., 2019). Patients in treatment for lymphoma who acquire COVID-19 should be monitored for the application of a drug, since many antineoplastic agents are substrates for CYP and their effectiveness may be affected. In addition, the genetic characteristics of patients can affect DDIs, and to compromise the CYP450 functioning (Daly, et al., 2018).

When it comes to drugs, pharmacokinetics must be strongly considered, especially when referring to critical diseases (El-Ghiaty, et al., 2020), because there is a possibility of increased toxicity or decreased drug efficacy when co-administered two drugs (DDI) (Olin, et al., 2019). Moreover, the clinical studies scarcity involving SARS-CoV-2 infected and lymphoma affected patients generates imprecise therapeutic conditions that can be misdirected. Thus, multidisciplinary studies in the field of health are necessary, including pharmacological research on the potential DDIs, drug safety and patient management (Riu-Viladoms, et al., 2019).

4. Conclusion

Most interactions between the drugs used in the chemotherapy of lymphomas and COVID-19 occur through alterations in the metabolism of the cytochrome P450 enzyme system or in the efflux transporter of the P-glycoprotein (P-gp). Drug interactions can put the patient at risk of serious adverse effects, as they can potentiate or reduce the effects of a drug, possibly to the point where it is totally ineffective, reducing the safety and effectiveness of the treatment and requires attention.

Studies that focus on DDIs among drugs used to treat COVID-19 and such lymphomas are still limited, and researches that considers the safety and efficacy of DDIs and their adverse reactions are needed. In order to outline the best treatment profile for patients with Hodgkin or non-Hodgkin lymphomas and affected by COVID-19, the pharmacology specialist is indispensable. Futhermore, even with all mandatory sanitary measures, personal effort is essential to prevent the SARS-CoV-2 transmission.

A more effective participation of pharmacists added to additional *in silico*, *in vitro* and *in vivo* studies that address the interaction between the drugs reported here are needed, also in view of their use aimed at other diseases. Thus, knowing the drugs helps health professionals to reflect on clinical intervention as well as promote studies in the area to increase the quality of health practices and the process of drug use.

Competing interests

The authors declare that they have no competing interests

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