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Research Article

Possible Interaction Between Drugs for COVID19 And Cancer Therapy

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Abstract:

At the end of 2019, a new disease was reported in Wuhan China and described such as severe acute respiratory syndrome (SARS). This new virus named SARSCoV-2 S is characterized by high infectivity among humans. Such disease can have no symptoms in some individuals, while in others can provoke flu like symptoms or acute respiratory distress syndrome, pneumonia, and death. At the end of January 2020, the World Health Organization and Public Health Emergency of International Concern declared a pandemic status. Many studies showed a high mortality rate in cancer patient infected by SARS-CoV-2 infection. In this context, the decision of a safe and effective treatment against COVID19 plays a crucial role crucial in these patients Therefore, important questions arose: Can the COVID19 therapies protect everyone and above all cancer patients? and which drug interactions can occur between cancer therapy and COVID19 treatment? In this regard, Covid-19 is a new disease and for this reason it will be necessary to modify constantly pharmacological treatment. In this scenario, the potential drug–drug interactions (DDI) in the cancer patients should be considered to evaluate the risks and benefits of drug combinations.

Key words: DDI, cancer patients, SARS-CoV2, antineoplastic agents, pharmacological interventions.

1. Introduction

At the end December 2019, severe acute respiratory syndrome coronavirus has infected about 560 million individuals around the world by the middle of February 2021 (WHO, 2022; Zhou et al., 2020).On March 3th 2024, data obtained revealed that since the start of the outbreak 774.834.251 individuals have been diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection globally, and 7.037.007 deaths have been reported by the WHO (https://data.who.int/dashboards/covid19/cases?n=c) (WHO, 2022). Many data suggested a significant acute respiratory distress syndrome and/or multiorgan failure can be developed in 14% to 19% of infected individuals, and in addition, approximately 35% to 50% of infected people can die from this disease. In this regard, cancer patients should be considered as a group at higher risk of serious and lethal complications of COVID-19. For example, many papers reported that the 30-days survival of cancer patients with COVID-19 infection can be to be 60%–70%. Moreover, cancer patients have a higher risk of dying of this disease because of the immunosuppression, increased comorbidities and, in cases of lung malignancy, underlying pulmonary compromise. Furthermore, it was observed that this virus can increase the risk of mortality among older cancer patients. In this context, treatments in oncology will become more complex by considering the heterogeneity of cancers and therapies. This pandemic has raised new challenges for oncologists, above all in the therapy decision-making process. Several chemotherapies include the combination of different injectable and oral drugs can provoke multiple side effects. In this regard, it is important to better evaluate the interaction between the chemotherapy regimens and the treatments for Covid-19. Specifically, a study carried out on cancer patients with Covid-19 examined different drugs treatment for COVID10 such as hydroxychloroquine, azithromycin, remdesivir, high-dose corticosteroids, and tocilizumab, taken alone and in combination (Rivera et al., 2020) The aim of this review is to analyze potential interactions pathway between antineoplastic agents and drugs used in COVID-19.

2. The therapy for COVID 19

Different drugs, developed for others infective disease, are repurposed in COVID-19 infection, and then approved by the Food and Drug Administration (FDA) Trivedi et al., 2020: Kumar et al., 2021) (Table 1). Among them, favipiravir and the lopinavir-ritonavir combination have been proven most

promising against COVID-19 treatment. Anti-malarial drug hydroxychloroquine (HCQ) showed good results against COVID-19, and it has been used frequently in combination with other drugs (Mitja and Clotet, 2020; Rismanba, 2020). Some anti-inflammatory and anti- antibiotics were also used either in combination or alone for the treatment of COVID-19 patients.

Table 1. Drugs used for COVID-19

Antiviral-drugs	Remdesivir, Favipiravir, Lopinavir, Ritonavir,
Others	Chloroquine, Hydroxy chloroquine, Ivermectin,
Anti-Inflammatory drugs	Baricitinib, Tocilizumab,
Antibiotics	Azithromycin, Rapamycin

2.1 Chloroquine/Hydroxycloroquine

Two anti-malarial chloroquine (CQ) and hydroxychloroquine (HCQ) have been considered as potential therapy against SARS-CoV2 virus (Colson et al., 2020). A clinical investigation was conducted in Guangdong, China, to evaluate the effectiveness of chloroquine (CQ) as a treatment for COVID-19 patients. The results of this study suggested that CQ could be a practical and efficient treatment choice among the many suggested ones for individuals with mild to severe SARS-CoV-2 infection. Patients treated with CQ had a more rapid restoration of pulmonary function compared to those treated with other antiviral medications, such as the two drugs e.g. lopinavir/ritonavir (an inhibitor of protease combination used to treat HIV infection (Huang et al., 2020). According to another clinical trial, CQ along with Hydroxychloroquine (HCQ) both shown promise in accelerating the duration of clinical improvement and boosting viral RNA negative in patients with mild COVID-19 infection (Lv et al.,2015). The findings of this randomized controlled study utilizing HCQ for the management of COVID-19 in Wuhan, China, showed that the drug successfully lowered fever and cough duration (Lv et al.,2015). These results imply that HCQ could be a therapy option for COVID-19 patients who are critically feeling unwell. In addition, clinical research involving severely sick COVID-19 patients receiving HCQ showed that HCQ treatment significantly decreased the probability of mortality in COVID-19 patients without causing any obvious negative effects (Yu et al., 2020). This study emphasizes the potentially life-saving value of HCQ therapy for seriously sick people who are infected with SARS-CoV-2. Furthermore, two studies showed that the chloroquine (CQ) and hydroxychloroquine (HCQ) were able to inhibit pneumonia exacerbation, by reducing the fever duration (Wang et al., 2020). In 2020, multiple trials have been registered (ClinicalTrials.gov 2020; Gautret et al., 2020; Hernandez et al., 2020; Huang et al., 2020). Nowadays, some authors pointed out that these drugs at high doses could induce severe side effects such as restrictive or dilated cardiomyopathy or ion system abnormalities such as atrioventricular and bundle-branch block (Asli et al., 2020) irreversible retinopathy (Nicolò et al., 2021), and hypoglycemia (Imanova et al., 2021; Alanagreh et al., 2020; Das et al., 2020; Dirim et al., 2020; Zhan et al., 2020).

2.2 Protease inhibitors

Different Protease inhibitors (PIs) such as atazanavir, ritonavir, lopinavir and nirmatrelvir/were used for treatment of COVID-19.

2,2.1 Lopinavir/Ritonavir

The Lopinavir was used in combination with ritonavir in COVID-19 patients. Lopinavir shows in vitro inhibitory activity against SARS-CoV-2, and Middle East respiratory syndrome (MERS) coronavirus (Choy et al., 2020; Sheahan et al., 2020; Wilde et al., 2014; Chen et al., 2004), In addition, one study, using in a marmoset model of MERS, showed that lopinavir–ritonavir combination was able to improve clinical, radiological, and pathological outcomes and decreased viral loads (Chan et al., 2015). Ritonavir is able to block P-glycoprotein, that pumps drugs out of the gut wall and back into the intestinal lumen, as well as CYP3A4 and CP450 isoenzymes that are involved in drug metabolism (Boffito, 2004). Reis et al. (2021) conducted a randomized clinical trial on 685 patients divided in three arms: 214 received hydroxychloroquine, 200 received lopinavir/ritonavir, while 227 patients received placebo. The data reported that there was no statistical difference in the risk of hospitalization between patients treated with hydroxychloroquine and those treated with lopinavir/ritonavir and additionally, there was no significant difference n terms of virological clearance and symptom resolution as assessed using the WURSS (Wisconsin Upper Respiratory Symptom Survey) scale. Cao et al (2020), in another controlled, randomized, open-label trial, showed that the results in the hospitalized adult patients with severe Covid-19 did not significantly provide a clinical outcome for lopinavir/ritonavir when compared with those of standard care alone. At the end, Pan et al (2021) analyzed the mortality of patients treated with lopinavir/ritonavir. In this trial, 1399 patients were treated with lopinavir/ritonavir, while 372 patients received standard care. The authors found that 148 patients of the first group and 146 patients of the second group died, respectively. Furthermore, 126 patients of the first group and 121 patients of the second group were ventilated, respectively. Therefore, treatment with lopinavir/ritonavir had no positive impact on mortality and ventilation initiation in COVID-19 patients.

2.2.2 Nirmatrelvir/Ritonavir

Nirmatrelvir and ritonavir are two antiviral protease inhibitors. Nirmatrelvir is able to block the 3CL pro enzyme in SARS-CoV-2, while ritonavir is able to block cytochrome P450 3A4 enzyme and, in this way it can elongate Nirmatrelvir presence in the body and increase its activity (Hammond et al., 2022). Furthermore, Nirmatrelvir can also inhibit the Mpro proteolytic activity in all different types of human coronavirus, which include alpha-coronaviruses (HCoV-NL63 and HCoV-229E) as well as beta-coronaviruses (MERS-CoV, SARS-CoV-1, SARS-CoV-2, HCoV-OC43, and HCoV-HKU1). This compound also shows strong antiviral activity against SARS-

CoV-2, MERS-CoV, HCoV-229E, and SARS-CoV-1 (Owen et a., 2021). Furthermore, infected patients at high risk can be treated with Nirmatrelvir after the beginning of the disease (JA OS. EUA 105 Pfizer, 2021). The EPIC-HR trial was performed at the time of delta variant pandemic. Arbel et al. (2022) evaluated nirmatrelvir effects in 3902 individuals at the time of Omicron pandemic. They found that this drug in patients ≥ 65 year was able to decrease death rate when compared to the control. In the case of young patients, it did not inhibit the course of the disease. Furthermore, in a in vitro study, Li et al. (2022) found that nirmatrelvir at low concentrations were able to block Omicron variant replication in infected Calu-3 cells. Furthermore, the Calu-3 cells were treated with the association of the serum of different vaccinated individuals and the drug and then such cellular line were exposed to either wild-type (WT) or Omicron form. The authors found that wild-type SARS-CoV-2 was unable to replicate in the serum-incubated cells while Omicron variant of the virus could also replicate at low levels after the addition of nirmatrelvir. In another study, Vangeel et al (2022) evaluated the nirmatrelvir antiviral activity for different SARS-CoV-2 variants of concern (VOCs) (alpha, beta, gamma, delta, and Omicron).. They showed that nirmatrelvir work well against all known VOCs, including Omicron. Furthermore, in this study, the authors reported that it some missense point mutations in SARS-CoV-1 such as 3CLpro may negatively impact the protease activity (Hashemian et al., 2023). These data were reported by Peluso et al. considering four consecutive cases from a post-COVID cohort analysis and treated with different regimens of nirmatrelvir (Peluso et al., 2022). In this regard, the first patient treated with antiviral therapy suffered a clinical rebound, while other two patients, treated with nirmatrelvir at 25 and 60 days after their COVID-19 symptoms, improved after this therapy. In addition, one study showed that mutations in Mpro proteins of SARS-CoV-2 variants. may cause resistance to nirmatrelvir (Iketani et al., 2023). At the time of Omicron pandemic, Najjar-Debbiny et al. (2023) carried out a study on adults who were experiencing COVID-19 for the first time and followed them for 28 days. These patients who received nirmatrelvir/ritonavir, showed a strong reduction in the death rate as well as the risk of progression into severe disease in comparison to control. In another study, Malden et al. (2022) evaluated the efficacy of this therapy on t 5287 patients treated with nirmatrelvir/ritonavir and then whether these patients needed care from the health system after 5 and 15 days from nirmatrelvir/ritonavir course. They found that 45 patients needed the health care system of whom six were hospitalized. Among the half of these 45 patients the authors found two risk factors such as age (≥65) and the presence of medical comorbidity. In another similar retrospective study, Shah et al. evaluated the results derived by 699,848 Americans with COVID-19 in the spring and summer of 2022, who were treated with nirmatrelvir/ritonavir. They showed that this combination of drugs decreased the rate of admission to hospital (Shah et a., 2023).

2.3 Favipiravir

This drug is able to inhibits RNA dependent RNA polymerase enzymes leading to prevention of virus replication (Furuta et al., 2009). It is metabolized by aldehyde oxidase (AO) and xanthine oxidase to its metabolite, T705M1, in liver and excreted to urine (Du and Chen, 2020). Its elimination half-life is about 2–5.5 with a protein binding of 54 % in plasma. Considering the genetic similarities of the SARS-CoV-2 and MERS-CoV-2, Favipiravir has emerged as a potential candidate for COVID-19 treatment. Clinical trials, including one in Shenzhen with 80 patients, demonstrated promising results. Patients in the Favipiravir group exhibited significantly shorter viral clearance times and improved chest imaging compared to the control group. Several multicentered randomized clinical studies supported Favipiravir's efficacy, particularly in ordinary COVID-19 patients and those with comorbidities like hypertension and diabetes, where it reduced fever and cough relief times (Batool et al., 2023; Bosaeed et al., 2022: Chen et al., 2021 Shinka et al., 2021; Cai et al., 2020). Clinical trials, including one in Shenzhen with 80 patients, demonstrated promising results. Patients in the Favipiravir group exhibited significantly shorter viral clearance times and improved chest imaging compared to the control group. Another multicentered randomized clinical study supported Favipiravir's efficacy, particularly in ordinary COVID-19 patients and those with comorbidities like hypertension and diabetes, where it reduced fever and cough relief times (Batool et al., 2023; Bosaeed et al., 2022: Chen et al., 2021 Shinka et al., 2021; Cai et al., 2020). . Another study reported a good result in COVID19 patients treated with a combination of favipiravir and tocilizumab. Solaymani-Dodaran et al (2021) compared the results obtained in different patients' groups: in the first group, patients were treated with favipiravir, the second group with lopinavir/ritonavir and the third group (control) with the standard therapy. The authors showed that 47 patients died (26, and 21 were treated with favipiravir and lopinavir/ritonavir patients, respectively). Furthermore, 56 patients treated with were transferred to ICU (31treated with favipiravir and 25 treated with the lopinavir/ritonavir) and 44 of them were intubated (26 in the favipiravir group vs 21 in lopinavir/ritonavir group). Specifically, the authors did not find significant differences in ICU admissions, duration of stay in hospital and bSpO2 changes during hospitalization between the Favipiravir and lopinavir/ritonavir groups. Furthermore, Zhao et al. (2020) evaluated the level of IL-6 in COVID-19 patients. They carried out a multicenter trial on 26 adults with COVID-19 and treated with favipiravir, and tocilizumab and the combination of these two drugs (combination group) for 14-days. They found that cumulative lung lesion remission rate was significantly higher in combination group as compared with favipiravir group after 14 days. Furthermore, they reported a higher mortality rate or an incidence of invasive mechanical ventilation in favipiravir group when compared with combination group or tocilizumab group. In conclusion, these data suggested that tocilizumab combined with or without favipiravir can effectively improve the pulmonary inflammation of COVID-19 patients and inhibit the deterioration of the disease. Dabbous et al. (Dabbous et al.,

2021; Dabbous et al., 2021) conducted two studies comparing favipiravir with chloroquine and hydroxychloroquine. In both studies, the authors did not find a significant difference between the favipiravir, and groups treated with chloroquine and hydroxychloroquine. Udwadia et al (2021) conducted a study to compare the addition of favipiravir treatment to supportive therapy. The data showed that it was necessary 5 days to stop spreading of virus when the patients were treated favipiravir vr 7 days in the case of supportive therapy. Furthermore, time to recovery from initial clinical symptoms was 5 days in patients treated with favipiravir vs 5 days in patients treated with supportive therapy. At the end, time to discharge from hospital was better in the favipiravir-treated group than the control group. Finally, Lou et al (2021) carried out a study considering antiviral activity from 3 groups where COVID19 patients were treated with the lopinavir/ritonavir or arbidol or darunavir/cobicistat and one control group. The result showed that there was no significant difference between the three groups in making the virus in patients negative at 14 days. Moreover, this drug has many side effects such as mild to moderate diarrhea, elevated liver enzymes, testicular toxicity, increased blood uric acid and decrease in neutrophil count.

2.4 Ivermectin

During, the SARS-CoV-2 pandemic, both observational and randomized studies have evaluated ivermectin as a treatment for, and as prophylaxis against, COVID-19 infection. Ivermectin, a commonly used drug for combating parasitic infections, has been the subject of substantial debate and research as a potential treatment option for COVID-19. Despite demonstrating antiviral properties in laboratory experiments, its effectiveness and safety in addressing COVID-19 continue to be contentious matters. The suggested mechanism of action for Ivermectin against COVID-19 involves its ability to hinder the replication of the SARS-CoV-2 virus within host cells. This is thought to occur by blocking crucial proteins that facilitate the virus's entry into cells and its replication. These initial observations sparked interest in repurposing Ivermectin for COVID-19 treatment. Nonetheless, clinical investigations into the efficacy of Ivermectin have produced inconsistent outcomes. Some small-scale trials have suggested potential benefits, such as reduced recovery times and lower mortality rates. However, these studies often had limitations, including small sample sizes, Specifically, a recent study found that ivermectin decreased deaths by 75% (Popp et al., 2022). Moreover, the National Institutes of Health in the United States recently reported that "there are insufficient data to recommend the use of ivermectin for the treatment of COVID-19 (NHI, 2021; WHO, 2021). Caly et al (2020) demonstrated that ivermectin was able to block the nuclear import of proteins os SARS-C0V-2 in vitro (Caly et al., 2020, Jans and Wagstaff, 2020) Other studies elucidated other mechanisms of inhibition of SARS-CoV-2 3CL pro activity (Mody et al., 2020; Anand et al., 2003), several anti-inflammatory effects (DiNicolantonio et al., 2020) and competitive binding of ivermectin with the viral S protein as shown in a silico study (Lehrer and Rheinstein, 2020). At the end, the half-life of this drug is around12−20 hours after administration (González Canga et al., 2008).

2.5 Remdesivir

Remdesivir, developed by Gilead Sciences Inc. in the United States, is an experimental nucleoside analog functioning as a competitive inhibitor of viral RNA-dependent RNA polymerase (RdRp). It undergoes a transformation within the body, turning into an active compound called GS-441524. Remdesivir was initially considered for the treatment of Ebola and has not yet received approval from the US Food and Drug Administration (FDA) or any other global drug regulatory authority. Its antiviral properties against RdRp have been observed in the context of viruses such as Ebola, MERS-CoV, SARS-CoV, as well as other coronaviruses including CoV-OC43, CoV-229E, and PDCoV. In a study. Wang et al (2020) carried out a randomized, double-blind, placebo-controlled trial on 237 COVID-19 patients that were divided in two groups 158 patients were treated with remdesivir and 79 with the placebo. In this case, the data reported that it did not improve clinical situation, and viral clearance in patients. Additionally, the authors observed a slightly better clinical improvement in patients treated with remdesivir within 10 days of symptom onset when compared with patients treated with placebo. Furthermore after 28 days, in the remdesivir group the mortality rate was had higher than the placebo group, but all deaths were not correlated to the intervention during the follow-up. In another trials, Spinner et al (2020) and Goldman et al (2020) showed that the effectiveness of remdesivir was very similar after 5 vor 10 days of therapy after 5 and 10 days. They reported different side effects such as nausea, hypokalemia, and headaches. Furthermore, after 28 days, mortality was around 1% in remdesivir group treated for 5 days, 2 % in in remdesivir group treated for 10 days, and 2% in the standard care group. Beigel et al (2020) conducted a controlled trial in 1062 adult COVIID 19 patients divided in two groups: 541 received remdesivir while 521 received placebo. The authors reported that patients treated with remdesivir had shorter recovery time, lower mortality, shorter hospital time and fewer serious side effects when compared with placebo group. Furthermore, another study (Rehman et al., 2021) evaluated the mortality in two different groups: 2743 patients received remdesivir, and 2708 control patients received standard local care. The authors observed that there were 301 fatalities the remdesivir-group and 303 in the control group. After randomization, 295 patients underwent ventilation initiation in remdesivir group and 284 in the control group. Furthermore, Kalil et al (2021) conducted a study considering the response in hospitalized COVID19 patients treated with the association of baricitinib plus remdesivir or remdesivir plus placebo. They found a clinical improvement and recovery time, in patient treated with baricitinib plus remdesivir when compared with patients treated with remdesivir alone. This drug is able to block RNA-dependent RNA polymerase (Al-Tawfiq et al., 2020: Gordon et al., 2020; Chen et a., 2019Tchesnokov et al., 2019; Mealey et al., 2003).

2,6 Tocilizumab

Tocilizumab, an immunosuppressive drug, has been investigated as a potential treatment for severe cases of COVID-19. Its primary target is the interleukin-6 (IL-6) pathway, which plays a vital role in the body's immune response and the development of inflammation. In severe COVID-19 cases, an exaggerated immune response, often referred to as a "cytokine storm," can result in harmful inflammation and lung tissue damage. Tocilizumab's mode of action involves blocking the IL-6 receptor, thus mitigating the inflammatory response. It has been utilized to manage the inflammatory symptoms associated with COVID-19, particularly in patients requiring mechanical ventilation or exhibiting systemic inflammation. Clinical trials have yielded diverse findings regarding the effectiveness of tocilizumab. While some studies suggest potential benefits such as reduced mortality and improved clinical outcomes, others have not demonstrated significant advantages. Variability in patient selection, the timing of administration, and dosing regimens may contribute to these discrepancies. Tocilizumab is typically reserved for severe COVID-19 cases, and its use continues to be refined as new research emerges. As our understanding of COVID-19's pathogenesis and treatment strategies advances, tocilizumab remains a valuable tool in medical practice, with ongoing studies aimed at determining its most appropriate applications in managing this complex disease.—A small-sample clinical trials performed in China (Yu et al., 2020) showed that p COVID-10 critically patients had recovery of 90% after a short period of the tocilizumab treatment. Thereafter, other case-control retrospective studies reported that c mortality rate in most critical COVID-19 patients with developed ARDS could decrease following tocilizumab therapy (Wadud et al., 2020) and could improve the survival outcome (Cellina et al., 2020; Zhang et al., 2020). Furthermore, patients with severe COVID-19 pneumonia and treated with tocilizumab had a reduced risk of invasive mechanical ventilation or death (Somers et . al., 2021). Different trials were performed such as RECOVERY (Horby et al.,2021), the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) platform (Gordon et al., 2021; Angus et a., 2020). the COVACTA (Rosas et al., 2021) and the EMPACTA studies (Salama et al., 2021) to evaluate the effeteness of tocilizumab on COVID19 patients. In this regard, the data among different groups of patients were resulted conflicting because of differences in timings of tocilizumab administration. Tocilizumab is an Ig G recombinant humanized monoclonal antibody that is able to block the receptor of IL-6 in order to avoid the cytokine storm that occurred in COVID19 patients because of level of IL-6 increase (Coomes et al., 2020).

2.7 Azithromycin

Azithromycin (AZM) is used in many different infections caused by bacteria. It was active in vitro against Ebola. An initial study evaluated the combination of two molecules, hydroxychloroquine and Azithromycin i to block SARS-CoV-2 replication in Vero cells at two different concentrations such as 5 and 10 μM (Andreani et al., 2020; 9 Touret et al., 2020). Moreover, another observational study suggested that the association between HCQ and AZM was able to improve virological clearance. Furthermore, different publications were released either favoring or discouraging the use of Azithromycin both with and without HCQ (Kamel et al., 2022; Gyselinck et al., 2021; Lammers et al., 2021; Tanriverdl et al., 2021; Albani et al., 2020; Arshad et al., 2020; Ayerbe et al., 2020; Cavalcanti et al., 2020: Echeverría-Esnal et al., 2020; Geleris et al., 2020; Guérin et al., 2020; Kuderer et al., 2020: Lauriola et al., 2020; Rosenberg et al., 2020: Sekhavati et al., 2020; Szente Fonseca et al., 2020). In summary, studies reported that this drug was not able to improve clinical situation in COVID19 patients.

3. Drug Interaction between COVID compounds and anticancer agents

This pandemic has provoked a significant trauma in the general population due to its effect on daily life (McIntyre and Lee, 2020; Liang et al., 2020; Islam et al., 2021). During this times, different studies reported cancer patients with SARS-CoV-2. In this regard, Liang et al. (2020) found that the COVID-19 infection rate was very high in cancer patients. In another study on cancer patients with infection, Zhang et al. (2020) observed high vulnerability to infection in these patients. As demonstrated by Lee et al (2021) a large trial study on 20.000 cancer patients, reported that a high risk of COVID-19 infection among cancer population especially in old and men patients. In this scenario, cancer patients should be undergone to standard treatments for COVID19 to avoid a severe infection. A recent systematic review and meta-analysis has reported that the death rate in cancer patient during active chemotherapy could be higher than normal patients since the combinations of COVID-19 drug and antineoplastic agents could potentially cause in loco interactions with significant adverse effects on patient outcomes. In this regard, Mario Jorge Sobreira da Silva and colleagues carried out a descriptive study to analyze potential drug–drug interactions (DDIs) between Covid-19-treatments and antineoplastic drugs (Sobreira da Silva et al., 2022). For this reason, they selected 34 drugs from a list published by the American Society of Health-System Pharmacists (ASHP) in May 2020. They decided to include 26 drugs for the COVID19 treatment (ascorbic acid, albuterol, alteplase, anakinra, atazanavir, azithromycin, baricitinib, chloroquine, colchicine, darunavir, epoprostenol, favipiravir, heparin, hydroxychloroquine, immunoglobulin, indomethacin, ivermectin, lopinavir/ritonavir, nitazoxanide, nitric oxide, oseltamivir, remdesivir, ruxolitinib, sirolimus, and tocilizumab) and 201 antineoplastic agents. The authors extracted the data by two different databases such as the Lexicomp® and Micromedex®, considering the interaction severity ("major" and "contraindicated") and interaction effects (pharmacokinetic and pharmacodynamic) results. They found 388 "major" or "contraindicated" drug-drug interactions and 91% of these interactions happened among eight drugs or combinations (baricitinib, lopinavir/ritonavir, atazanavir, darunavir, azithromycin, chloroquine, hydroxychloroquine, and sirolimus). In the case of antineoplastic agents, they found a potential interaction with tyrosine kinase inhibitors (accounting

for 46.4% of all interactions), and other followed antineoplastic agents (13.9%) and plant alkaloids (10.8%). Specifically, this study reported that atazanavir and lopinavir/ritonavir can impact the treatment of all common types of cancer. The highest number of DDIs were recorder in hematologic malignancies—lymphoid leukemia (10.0%) and lymphoma (9.2%); solid tumors—genitourinary (14.5%), lung (13.3%), and breast (12.2%) cancer. Furthermore, an increased plasma concentration of the medicine used to treat Covid-19 was observed in 164 of DDIs, while an increased plasma concentration of the antineoplastic agent was found in 100 of DDIs. Furthermore, the authors detected increased risk of changes in cardiac parameters in 98 (23.6%) of the potential DDIs. In this regard, the increasing number of new cancer cases, the different chemotherapy treatment, the high transmissibility of SARS-CoV-2, and a wide variety of drugs for this virus is becoming a significant issue in drug interaction Today, there are few studies since that examine the potential interactions between dugs for COVID 19 and different chemotherapy treatment but it is necessary to better understand this issue to avoid the potential risks for cancer. The drugs used for COVID-19 infection (such as chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir, atazanavir, favipiravir, and tocilizumab) are metabolized by different cytochromes such as P450, CYP2C9. Specifically, CYP2C9 metabolizes 15–20% of drugs (Fekete et al., 2021), while cytochrome P450s are responsible for metabolism of endogenous and exogenous substances, involved in different diseases such as viral infections, cancer, diabetes (Wu et al., 2019).

Chloroquine (CQ) and its derivatives such as hydroxychloroquine (HCQ) play a crucial role in the therapy for malaria. In addition, they are also approved for some autoimmune diseases such systemic lupus erythematosus, but their use is associated with severe adverse effect such as cardiotoxic effects, liver and kidney problems, nerve cell damage and low blood sugar (hypoglycaemia). Furthermore, high doses can cause significant side effects, such as abnormal electrical activity that affects the heart rhythm (QT-prolongation). In case of antineoplastic drugs, some studies reported dangerous drug interaction. as summarized in Table 2 (Rezaee et al., 2021; Giudicessi et al., 2020; Aralen (chloroquine) package insert, 2018).

Table2. Interaction with different antineoplastic agents and chloroquine

Drug for COVID-19	Antineoplastic agents	DDI	Side effects	Recommandations	References
Chloroquine	Tamoxifen	Inhibition of CYP2D6 Sostituire	Tamoxifen may enhance the retinopathy of chloroquine. Potential increased risk of QT prolongation		(Rezaee et al., 2021)
	Ceritinib	The increase of QT interval prolongation	Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Crizotinib	The increase of QT interval prolongation	Potential increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Dasatinib	The increase of QT interval prolongation	. Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Encorafenib	The increase of QT interval prolongation	Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)

	Gemtuzumab ~~and~~ ozogamicin	The increase of QT interval prolongation	Potential Increase of QT interval prolongation -	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Inotuzumab Ozogamicin	The increase of QT interval prolongation	Potential Increase of QT interval prolongation -	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Aralen (chloroquine) package inser, 2018)
	Ivosidenib	The increase of QT interval prolongation	. Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Lapatinib	The increase of QT interval prolongation	Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Lenvatinib	The increase of QT interval prolongation	Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Nilotinib	The increase of QT interval prolongation	Potential Increase of QT interval prolongation…	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Osimertinib	The increase of QT interval prolongation	Potential Increase of QT interval prolongation .	In the case of QT prolongation, it is necessary to change osimertinib therapy with dose reduction or discontinuous therapy	(Giudicessi et al., 2020)
	Panobinostat	The increase of QT interval prolongation	Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Ponatinib	The increase of QT interval prolongation	There is an increased risk of retinal toxicity	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	Aralen (chloroquine) package inser, 2018)
	Ribociclib	The increase of QT interval prolongation	- Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)

	Sunitinib	The increase of QT interval prolongation	- Potential Increase of QT interval prolongation.	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency	(Giudicessi et al., 2020)
	Trametinib	The increase of QT interval prolongation	There is an increased risk of retinal toxicity		Aralen (chloroquine) package inser, 2018)
	Vandetanib	The increase of QT interval prolongation	- Potential Increase of QT interval prolongation.	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine. frequency. An interruption of vandetanib therapy or dose reduction could be necessary for QT prolongation.	(Giudicessi et al., 2020)
	Vemurafenib	The increase of QT interval prolongation	- Potential Increase of QT interval prolongation	It is necessary to monitor parameters and precautions with an electrocardiogram at baseline to assess initial QT interval and determine.frequency	(Giudicessi et al., 2020)

Lopinavir/Ritonavir form a complex that interacts with cytochrome (CYP) P450 enzyme system. Such sistem is composed by family of metabolic enzymes that are involved i metabolism of many substances. Specifically, both drugs or their combination can cause an increased plasma concentration of certain medications by inhibiting cytochrome P350. In particular, ritonavir is able to inhibit CYP3A4 clearing to toxic concentration of the co-administered medication (Berretta et al., 2016; Rudek wt al., 2011; Makinson et al., 2010). This inhibition causes hypotension, thrombosis, increased bleeding events, sedation and respiratory depression, and drug toxicity when there is thew combination with CYP3A4-mediated medications. (Makinson et al., 2010). Furthermore, another pharmacokinetic variable affected by ritonavir is the P-glycoprotein (P-gp) (Makinson et al., 2010). In addition, Lopinavir is metabolized by CYP3A4, while the ritonavir is a able to inhibit CYP3A4, and so their combination increases in the effect of lopinavir; and therefore, lopinavir cannot be used alone (Berretta et al., 2016; Rudek wt al., 2011; Makinson et al., 2010). Ritonavir, used in combination with nirmatrelvir (Paxlovid, manufactured by Pfizer), is considered an inducer of CYP2C9 (Lemaitre et al., 2022) as well as an inhibitor of CYP2C9 (Chary et al., 2023). For instance, Nilotinib is used in patients affected by chronic myeloid leukemia (CML), and it is metabolized by CYP3A. In this regard, the HIV patients with CML were treated with the combination of nilotinib and ritonavir and this therapy can cause different drug interactions through CYP3A inhibition or induction. In a study, the authors evaluated this drug interactions using human hepatocytes and then they compared the potential interactions with those of ketoconazole or rifampin (CYP3A inhibitor and inducer, respectively). First, hepatocytes were treated with vehicle, ritonavir, ketoconazole or rifampin for 5 days. After this time, the cells were incubated with nilotinib for additional 24–48 hours. Following this incubation, the authors found that the intrinsic clearance of nilotinib was decreased 5.8- and 3.1-fold by ritonavir and ketoconazole. respectively (Pillai et al., 2014). Other interactions are showed in Table 3 (Baburaj et al., 2021).

Table 3 Interaction with different antineoplastic agents and protease inhibitors (lopinavir/ritonavir and ritonavir/nirmatrelvir)

Antiviral Drug	Antineoplastic agents	DDI	Side effects	References
Lopinavir/ritonavir	Afatinib	Inhibitor P-glycoprotein	Increase of the plasma afatinib concentration o	(Baburaj et al., 2021)
	Brigatinib	inhibitor of CYP3A4		(Baburaj et al., 2021)
	Cabozantinib	Strong inhibitor of CYP3A4	Increase of cabozantinib concentrations	(Baburaj et al., 2021)

	Ceritinib	inhibitor of CYP3A4	Increase of ceritinib concentration	(Baburaj et al., 2021)
	Crizotinib	inhibitor of CYP3A4	Increase of crizotinib concentration	(Baburaj et al., 2021)
Ritonavir/ Nirmatrelvir	EGFR Inhibitors			
	Gefitinib	inhibitor of CYP2C19 and 2D6	Possible increase of the concentration of Ritonavir/Nirmatrelvir. Cutaneous adverse drug reactions, and gastrointestinal effects	(FDA-Iressa, 2018)
	Osimertinib	It is an inducer and an inhibitor of CYP 3A4	Cutaneous adverse drug reactions, and gastrointestinal effects	(FGA, TAGRISSO. 2015)
	Furmonertinib	inducer of CYP 3A4	Cutaneous adverse drug reactions, and gastrointestinal effects	(Zou et al., 2022))
	Sunvozertinib	inducer of CYP 3A4	Cutaneous adverse drug reactions, and gastrointestinal effects	(ClinicalTrials.gov. (Sunvozertinib) 2022)
	Mobocertinib (EGFR Exon 20 Insertion)	weak inducer of CYP 3A4	increased risk of adverse events (e.g., interstitial lung disease [ILD], pneumonitis, cardiac toxicity, and diarrhea	(FDA,EXKIVITY 2021)
	Tucatinib (HER2 – HER4 Inhibitors)	a strong inhibitor of CYP 3A4	Possible increase of the concentration of Ritonavir/ Nirmatrelvir. It can be associated with adverse effects	(FDA, TUKYSATM, 2020)
	Neratinib (HER2 – HER4 Inhibitors	is not an inhibitor or an inducer of CYP 3A4		https://covid19-druginteractions.org/interactions/23348
	Crizotinib (ROS1 Inhibitors)	inhibitor of CYP3A4	Possible increase of the concentration of Ritonavir/ Nirmatrelvir	(FDA, XALKOR, 2021)
	Entrectinib (ROS1 Inhibitors)	inhibitor of CYP3A4	Possible increase of the concentration of Ritonavir/ Nirmatrelvir. Adverse effects such as hepatotoxicity, QTc prolongation, ILD, and visual loss	(FDA, ROZLYTREK, 2019)
	Repotrectinib (ROS1 Inhibitors)	inhibitor of CYP3A4	Possible increase of the concentration of Ritonavir/ Nirmatrelvir	DDI data limited
	Taletrectinib (ROS1 Inhibitors)	neither an inducer or inhibitor of CYP 3A4		- DDI data limited ((Cleveland Clinic, 2022)
	Capmatinib (MET Inhibitors)	not inducer of inhibitor of CYP 3A4		(FDA, TABRECTATM, 2020))
	Tepotinib (MET Inhibitors)	is not inducer of inhibitor of CYP 3A4		https://www.covid19-druginteractions.org/
	Selpercatinib (RET Inhibitors)	inhibitor of CYP 3A	Possible increase of the concentration of Ritonavir/ Nirmatrelvir	(FDA, RETEVMOTM, 2020)

	Pralsetinib (RET Inhibitors)	weak inhibitor of CYP 3A4	Possible decrease of the concentration of Ritonavir/ Nirmatrelvir	(FDA, GAVRETO 2020)
	MEK/BRAF Inhibitors			
	. Cobimetinib	is inhibitor of CYP 3A4	Possible increase of the concentration of Ritonavir/ Nirmatrelvir	(FDA, COTELLIC, 2015)
	Vemurafenib	is inhibitor of CYP3 A4	Possible increase of the concentration of Ritonavir/ Nirmatrelvir	(FDA ZELBORAF, 2017)
	Encorafenib	is inducer of CYP 3A4	Possible decrease of the concentration of Ritonavir/ Nirmatrelvir	(FDA, BRAFTOVI, 2018)
	Dabrafenib	is inducer of CYP 3A4,	Possible decrease of the concentration of Ritonavir/ Nirmatrelvir	(FDA, TAFINLAR. 2018)
	Trametinib	is not an inducer or inhibitor of CYP 3A4		(FDA, MEKINIST, 2018)
	Larotrectinib (NTRK Inhibitor	is inhibitor of CYP 3°4	Possible increase of the concentration of Ritonavir/ Nirmatrelvir	(FDA, VITRAKVI , 2021)
	Cabozantinib (Multiple-Target TKIs	is not known as an inhibitor or inducer of CYP 3A4		(FDA, CABOMETYX, 2019)
	Anlotinib (Multiple-Target TKI)s	is inhibitor of CYP 3A	Possible increase of the concentration of Ritonavir/ Nirmatrelvir	(Sun et al., 2016) (Zhong et al., 2018)
	Sotorasib (KRAS p.G12C Mutations)	is not known as an inhibitor or inducer of CYP 3A4		(FDA, LUMAKRAS, 2021)
	Adagrasib (KRAS p.G12C Mutations)	induces and inhibits CYP 3A4 enzymes		https://www.mayoclinic.org/drugs-supplements/nirmatrelvir-and-ritonavir-oral-route/precautions/drg-20528231?p=1
	Alectinib ALK Inhibitors	neither inhibitor nor inducer of CYP 3A4		(Azanza et al., 2022)
	Brigatinib ALK Inhibitors	neither inhibitor nor inducer of CYP 3A4		(FDA, ALUNBRIG, 2020)
	Lorlatinib ALK Inhibitors	is an inducer of CYP 3A4	Possible increase of the concentration of Ritonavir/ Nirmatrelvir with adverse effects when they are taken together. Furthermore, patients should be monitored for nausea and constipation	(FDA, LORBRENA, 2021)

The combination of ritonavir with nirmatrelvir can increase plasma concentrations when it is used in association with different EGFR Inhibitors such as Gefitinib, Erlotinib, Afatinib, Osimertinib, Aumolertinib, Furmonertinib, Dacomitinib, Sunvozertinib, Lazertinib Mobocertinib through CYP3A4 inhibition (ClinicalTrials, 2022: Zou et al.,2022; FDA-Iressa, 2018; FDA, EXKIVITY 2021; FDA, TAGRISSO, 2015). For this reason, this combination can increase moderately the concentrations of these TKIs. causing the side effects. In the case of ROS1 Inhibitors, Crizotinib, entrectinib, and repotrectinib could increase the concentrations of ritonavir/nirmatrelvir by CYP 3A4 inhibition with a significant risk of adverse effects. Specifically, being both crizotinib and entrectinib major substrates of CYP 3A4, their administration with ketoconazole and itraconazole increased the AUCs about 216% for crizotinib and 500% for entrectinib. In this case, this

drug become most vulnerable to CYP 3A4 inhibition due to the combination ritonavir/nirmatrelvir, causing significant sidee effects (hepatotoxicity, QTc prolongation, ILD, and visual loss) ((Cleveland Clinic, 2022; FDA, XALKOR, 2021; FDA, TUKYSATM, 2020 FDA, ROZLYTREK, 2019). For MET Inhibitors such as capmatinib and tepotinib (Major substrates of CYP 3A4), the coadministration of ritonavir/nirmatrelvir can lead to a considerable risk of adverse events (e.g., ILD, hepatotoxicity, photosensitivity) (FDA, TABRECTATM, 2020). Besides, for RET Inhibitors (Selpercatinib, Pralsetinib - major substrates of CYP 3A4) it is possible to hypothesize an increased risk of adverse effects such as hepatotoxicity, QTc prolongation, hemorrhagic events, impaired wound healing); (FDA, GAVRETO 2020; FDA, RETEVMOTM, 2020). Among MEK/BRAF Inhibitors, Dabrafenib (a major substrate of CYP 3A4) or NTRK Inhibitor such as Larotrectinib (a major substrate of CYP 3A4)) or Cabozantinib (Multiple-Target TKI) the co-administration with ritonavir/nirmatrelvir could trigger strong side effects (e.g., diarrhea, nausea, fatigue, and electrolyte abnormalities (including dizziness, cognitive impairment, mood disorders, sleep disturbances), fractures, and hepatotoxicity (FDA, COTELLIC, 2015). Other studies are reported in Table 3 (Azanza et al., 2022; FDA, LORBRENA, 2021; FDA, LUMAKRAS, 2021; FDA, VITRAKVI, 2021; FDA, ALUNBRIG, 2020; FDA, CABOMETYX, 2019; FDA, BRAFTOVI, 2018; FDA, MEKINIST, 2018; FDA, TAFINLAR. 2018; Zhong et al., 2018; FDA ZELBORAF, 2017; Sun et al., 2016)

Favipiravir, antiviral substance that blocks RNA-dependent RNA polymerase, is mainly eliminated through aldehyde oxidase and xanthine oxidase enzymes and for this reason, it can cause hepatotoxicity. In addition, it is an inhibitor of CYP2C8 (152) and therefore it may increase anticancer drug metabolism (such as dabrafenib and enzalutamide) through inhibition of CYP2C8 (Du and Chen, 2020). Furthermore, it can cause the CYP3A4 induction that, in turn, could lead to CYP3A4 increased activity for up to 1 week after discontinuation. Another study reported that this drug was able to inhibit the Aldehyde oxidase (Du and Chen, 2020), and in this case, its use in cancer patients treated with tamoxifen or CYP2C8 substrates like paclitaxel (Aldehyde oxidase inhibitors) should be choose with caution (152). Moreover, a case report described a patient with metastatic osteosarcoma who was treated with high dose methotrexate, and favipiravir was used for suspicion of SARS-CoV2 infection. After 12 hours from the treatment, the patient showed toxic hepatitis due to incresed levels of liver enzymes caused by favipiravir-methotrexate interaction (Du and Chen, 2020).

The absorption, distribution and elimination of ivermectin occurs through P-glycoprotein (Demir et al., 2022). This drug is able to inhibit P-glycoprotein causing change the p-glycoprotein ABCB1 substrate (Ménez et al., 2012). The common side effects after its use are skin rash, fever, headache, nausea and dizziness. Furthermore, chemotherapeutic drugs that are metabolized by CYP3A4 and induce or inhibit P-glycoproteins can cause several interactions with ivermectin (Jiang et al., 2019; Mealey et al., 2003). Furthermore, in one study, the authors reported that he combination between paclitaxel and Ivermectin showed the highest cytotoxic effect and the strongest synergism for both HGSC chemo-resistant cell lines, resulting in a chemotherapeutic effect superior to both drugs alone. Moreover, results for OVCAR8 PTX R P (Carboplatin and Paclitaxel-resistant) cells were even more promising than OVCAR8 (Carboplatin-resistant), considering the synergistic combination (Nunes et al., 2022),

Unfortunately, for Remdesivir here are not any data about the drug pharmacokinetic and drug-drug interaction with neoplastic agents.

Many in vitro studies reported that tocilizumab is able to downregulate CYP (CYP3A4, CYP2C9, CYP2C19, and CYP1A2) enzymes by IL-6, which may interact with substances that are a substrate for these enzymes. Furthermore, the combination of tocilizumab with other drus requires a monitoring or 1–2 months after its discontinuation because of of long half-life of this drug to contro potential interactions. Different adverse effects were reported for this drug such as upper respiratory tract infection, neutropenia, headache, hypertension, alanine amino-transferase elevation and lipid profile changes. Some studies reported mild reaction in infusion site (Sheppard et al., 2017; Oldfield et al., 2009). One study showed that tocilizumab had no effect on QT interval (Grange et al., 2011). Another study reported that the administration of tocilizumab has no effect on MTX pharmacokinetic in patients with rheumatoid arthritis (Schmitt et al., 2016). Furthermore, increasing the level of IL-6 is the consequence of blocking IL-6 receptors by this drug. and this leads a decreased CYP450 activity decrease. In this regard, the co-administration of tocilizumab with other agents that metabolized by CYP450 should be considered with caution (Schmitt et al., 2011). Moreover, its use in cancer patients is an important issue being an immunosuppressive agent. In addition to rheumatoid arthritis therapy, the drug is also used to block cytokine release syndrome, a side effect of CAR-T anticancer therapy (Roche Pharma, A. RoActemra, 2013). Furthermore, in a study, Xu et al. (2023) showed that tocilizumab either alone or in combined with anlotinib in four osteosarcoma (OS) anlotinib-resistant cell lines, was able to block the tumor progression by inhibiting STAT3 expressions. The IL-6 expression level was high in patients with OS and it is assocciated cowith poor prognosis, but in this case, tocilizumab could reverse anlotinib resistance in OS by IL-6/STAT3 pathway.

At the end, Azithromycin has many interactions with neoplastic agents, especially those used to treat advanced lung cancer with activating mutations (EGFRIs afatinib and osimertinib; ALK—crizotinib; KRAS—dabrafenib and vemurafenib) breast cancer (lapatinib and ribociclib) and other types of solid m tumors involving mult-ikinase inhibitors (lenvatinib, sorafenib, sunitinib, and vandetanib) (Gay et al., 2017). This interaction could increased the risk of changes in cardiac parameters (Akbulut and Urun, 2019). However, several studies demonstrated that azithromycin could cause a sugnificant anti-proliferation effect by triggering apoptosis in HeLa cells and SGC-7901 cancer cells (Zhou et al., 2012). In addition, it has been reported that antibiotics could negatevely impact tumor

growth by targeting mitochondria and eradicating cancer stem cells (Lamb et al., 2015). Furthermore, the antiproliferative and apoptotic effects of azithromycin was showed in different cancer cells (Hassan et al., 2022; Mukai et al., 2016; Moriya et al., 2013). Moreover, this drug suppressed lung cancer growth of A549 xenograft-bearing severe combined immunodeficient mice (Li et al., 2017). Another study reported that azithromycin was able to interact with TRAIL in nude mice with HCT116 colon xenografts (Qiao et al., 2018). Chu et al. showed that azithromycin t administration in patients with advanced non-small lung cancer and affected by Chlamydia pneumonia and under treatment with paclitaxel and cisplatin improved the 1year survival rate 75/ versus45% (Chu et al., 2014).

4. Conclusions

The potential DDIs between viral drugs and antineoplastic agents should be a crucial issue to avoid the potential toxicity and the amplification of these effects due to interactions. In this regard, it is important to consider that cancer patients are more vulnerable to pharmacokinetic impacts induced by potential DDIs. due to their system impairment. One study (Griva et al., 2021) underlined the correlation between cytotoxic chemotherapy and higher Covid-19 severity. In this scenario, oncologists should know both positive and negative effects for decision-making in the treatments. Moreover, the absence of drug benefits against COVID19 is an important issue in clinical practice to avoid the risk outweighs the benefits.

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Competing interests

The authors declare that they have no competing interests.

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