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Considerations for interactions of drugs used for the treatment of COVID-19 with anti-cancer treatments

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ABSTRACT

SARS-CoV2 infection is an emerging issue worldwide. Cancer patient are at increased risk of infection compared to general population. On the other hand, these patients are at major risk of drug interactions caused by renal and hepatic impairment background. Because of the long-term use of chemotherapy drugs, drug interactions are important in these patients especially with SARS-CoV2 treatments now. This paper is review of reported drug interactions of current treatments for COVID-19 and anticancer agents.

1. Introduction

The novel coronavirus (SARS-CoV2) has caused a growing pandemic and global issue now (Zhou et al., 2020). Cancer patients are at a greater risk of catastrophic outcomes of Coronavirus infectious disease 2019 (COVID-19) because of the older age, immunosuppressive condition and combined comorbidity. Cancer patients may become infected by SARS-CoV2 during chemotherapy or may need to receive chemotherapy after the resolution of their disease and receiving coronavirus treatment (Wang and Zhang, 2020).

Here we reviewed drug interactions of current covid-19 drugs with antineoplastic agents. Montamat SC et al., said that the risk of drug interactions is higher in cancer patient due to their underlying disease, older age and consumption of multiple medications (Montamat et al., 1989). The current paper is a review of the reported and expected drug interactions of current treatments for COVID-19 and anticancer agents.

2. Mechanisms of interaction

Drug-drug interactions (DDIs) commonly happen when two drugs with DDIs administered before 4–5 half-lives of one of them (Ito, 2011). DDIs can cause three results: decreased therapeutic effect/adverse effects, enhanced therapeutic effect/adverse effects or a new side effect that does not occur with each drug separately. In pharmacodynamic interaction, both drugs affect the same physiologic pathway (Blower et al., 2005). This effect can be inhibitory or inducible.

Pharmacokinetic interaction happens when one drug influences other drug's absorption, distribution, metabolism or excretion (Blower et al., 2005). Drugs may affect the GI motility or PH, serum albumin concentration which can affect another drug absorption or distribution (Blower et al., 2005). Cytochrome P450 (CYP) with more than 50 isoenzymes is responsible for most of drug metabolism in liver. One drug can stimulate or inhibit its own CYP isoenzyme or other isoenzymes with further influencing the metabolism of other drugs that are metabolized with the same isoenzyme (Zhang et al., 2009). Another site of drug interactions occurs at P-glycoprotein that plays an important role in transporting drugs into cell on the cell membrane (Blower et al., 2005; Zhang et al., 2009).

3. Common therapeutic regiments for COVID-19

The most common proposed treatments for COVID-19 include chloroquine and hydroxychloroquine, azatinavir/ritonavir, lopinavir/ritonavir, remdesivir, tocilizumab and favipiravir (Baden and Rubin, 2020a, 2020b; Cascella et al., 2020; Dong et al., 2020; Guo et al., 2020).

3.1. Chloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are both 4-aminoquinoline agents that historically known as antimalaria drug from 1940s (Verbaanderd et al., 2017). These drugs have been used for treatment of rheumatoid arthritis, lupus erythematous, AIDS and

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recently COVID-19 (Ito, 2011; Solomon and Lee, 2009). Additionally, there are several in vivo and in vitro studies that confirm the anticancer effect of both CQ and HCQ. The most prominent evidences are three phase 3 clinical trials that used CQ during glioblastoma multiform with carmustin or temozolomide and showed positive results with added CQ. There are other phase 1–2 trials of addition the CQ to other chemotherapy regimens with hopeful results (Manic et al., 2014).Terminal elimination half-life of CQ is about 1–2 months and of 50 days for HCQ (Verbaanderd et al., 2017).

Short term use of CQ and HCQ is rarely associated with major side effects but serious side effects such as cardiomyopathy, irreversible retinopathy, myelosuppression and hypoglycemia have been reported after long-term use (Verbaanderd et al., 2017). Among the most serious adverse effects are cardiac side-effects such as atrioventricular block, bundle branch block, cardiac arrhythmia, cardiac failure, cardiomyopathy, electrocardiographic (ECG) changes including flattened T wave, T wave inversion, prolonged QT interval, widened QRS complex, hypotension, torsade's de pointes, ventricular fibrillation and ventricular tachycardia (Page et al., 2016).

Tamoxifen, an antiestrogen agent, is administered for breast cancer patients who needs to take it for years (Regan et al., 2016). CQ decrease the level of tamoxifen by CYP2D6 inhibition effect (Blower et al., 2005; Marmor et al., 2016). Whether consuming concurrent CQ or HCQ could affect the efficacy of tamoxifen in breast cancer patients is not clear but should be considered.

With regard to anti emetic drugs physicians should be noted that, granisetron is a safe antiemetic agent to be used concurrently with HCQ or CQ because unlike ondansetron, it does not appear to affect any CYP isoenzyme (Blower et al., 2005).

Ado-Trastuzumab Emtansine (TDM1) that is used to treat HER2-positive metastatic breast cancer, also metabolized largely by CYP3A4 but don't have any effect on this enzyme. (Ballantyne and Dhillon, 2013) We summarized main interactions of this drug with anticancer medicines (Table1).

3.2. Protease inhibitors

Protease inhibitors (PIs) such as atazanavir, ritonavir, lopinavir have been for treatment of COVID-19 (Baden, Lindsey R. and Rubin, Eric J., 2020). Lopinavir is used in combination with ritonavir- Kaletra- to increase the lopinavir's bioavailability (Eckhardt and Gulick, 2017). Reported half of lopinavir/ritonavir and atazanavir/ritonavir are 2–7/3 − 4 h, 8–9/5 − 6 h, respectively (Boffito et al., 2008; Chandwani and Shuter, 2008). About 85–95 % of these drugs bind to plasma proteins and metabolized in liver mainly by CYP3A4 isoenzyme (Makinson et al., 2010). Lopinavir is metabolized by CYP3A4 and on the other hand ritonavir is a potent inhibitor of CYP3A4, so the coadministration of them leads an increase in the effect of lopinavir; therefore, lopinavir is not used alone (Berretta et al., 2016; Makinson et al., 2010; Rudek et al., 2011).

Atazanavir, lopinavir/ritonavir also associated with Q-T interval prolongation so should be prescribed with caution with drugs with the same side effect such as tamoxifen, anthracyclines, dasatninb, lapatinib, nilotinib and sunitinib (Table 2) (Kebriaei et al., 2018) (DeRemer et al., 2008; Johnson et al., 2010; Lee et al., 2010; Pillai et al., 2014).

3.3. Favipiravir

Favipiravir is a pyrazine analog, originally made in Japan, oseltamivir resistant influenza (Furuta et al., 2013). The drug inhibits RNA-dependent RNA polymerase enzymes leading to prevention of virus replication (Furuta et al., 2009). The elimination half-life is about 2–5.5 with a protein binding of 54 % in plasma and metabolized by aldehyde oxidase (AO) and xanthine oxidase to its metabolite, T705M1, in liver and excreted to urine.(Du and Chen, 2020) Dose adjustment based on hepatic impairment is not needed however there is not enough humanized study about it (Du and Chen, 2020). The proposed dose for COVID-19 is the loading dose of 3200 mg on day 1 and maintenance dose of 1200 mg on day 2 − 14 (Du and Chen, 2020). Main side effects of favipiravir include mild to moderate diarrhea, elevated liver enzymes, testicular toxicity, increased blood uric acid and decrease in neutrophil count (2014). The rate of Q-T prolongation is low (8%) (2014). There is limited clinical data about DDIs and metabolism of favipiravir. In vivo study showed inhibitory effect of favipiravir on CYP2C8 isoenzyme (2014). As well as, other study revealed favipiravir inhibits AO (Du and Chen, 2020). So, more caution was necessary when used AO inhibitors such as tamoxifen or CYP2C8 substrates like paclitaxel with favipiravir (2014).

3.4. Ivermectin

Ivermectin is a broad spectrum antiparasitic agent that recently reported to have in vivo effect on SARS-CoV2 virus with 98 % elimination rate of virus RNA in or out of cells (Caly et al., 2020). It is used by oral or subcutaneous route and metabolized in liver by CYP3A4 isoenzyme (Canga et al., 2008; Zeng et al., 1998). Ivermectin binds to

Table 1
Chloroquine DDIs:

Covid-19 drug	Type of interaction		Result
Chloroquine	Q-T interval prolongation	Apalutamide, Leuprolide, Goserelin, Triptorelin,(Garnick, 2005) Eribulin (Perry, 2011), Ribociclib (Syed, 2017), Inotuzumab (Kebriaei et al., 2018), Gemtuzumab (Selby et al., 2019), Lenvatinib(Frampton, 2016), Dasatinib (Keam, 2008), Nilotinib (Kim et al., 2012), Cabozantinib and Ceritinib (Shah and Morganroth, 2015), Methadone (Barkin et al., 1998) Oxaliplatin(Chang et al., 2013) Ondansetron(Charbit et al., 2005)	Increase Q-T prolongation probability
	CYP3A4 induce	Apalutamide(Pérez-Ruixo et al., 2020), Ivosidenib (Pérez-Ruixo et al., 2020), Fedratinib (Xu) Dabrafenib(Ballantyne and Garnock-Jones, 2013), Encorafenib(Ballantyne and Garnock-Jones, 2013)	Decrease the level of CQ
	CYP3A4 inhibit	Idelalisib(Ballantyne and Garnock-Jones, 2013), Crizotinib(Forde and Rudin, 2012), Fedratinib(Xu et al., 2014), Dasatinib(Haouala et al., 2011), Abiraterone(Benoist et al., 2016), Bicalutamide(Meulenbeld et al., 2013), Aprepitant(Majumdar et al., 2003), Imatinib (Majumdar et al., 2003)	Increase the level of CQ
	CYP2D6 inducers	–	–
	CYP2D6 inhibitors	Dacomitinib(Bello et al., 2012), Abiraterone(Yang, 2011), Ondansetron(Blower et al., 2005), Methadone(Wu et al., 1993)	Increase the level of QC
	Pharmacodynamic synergism	All chemotherapy agents	Myelosuppression
	Pharmacodynamic antagonism	Sipuleucel-T(Cooper and Magwere, 2008; Plosker, 2011)	
	Effect on distribution	MTX(Blower et al., 2005)	

Table 2
Protease inhibitors DDIs:

Covid-19 drug	Type of interaction		Result
Protease inhibitors* (Makinson et al., 2010; Pasin, 2015; Rudek et al., 2011)	–	Platinum	No effect
	Inhibition of CYP3A4	Taxans	Increase the level of docetaxel
	Inhibition of CYP3A4	Vincaalkaloids	Increase the level vincaalkaloids
	–	Gemcitabine	No effect
	–	Topotecan	No effect
	Inhibition of CYP3A4	Irinotecan	Increase the level of irinotecan
	–	Pemetrexed	No effect
	–	Bevacizumab	No effect
	–	Cetuximab	No effect
	Inhibition of CYP3A4	Erlotinib	Increase the level of erlotinib
	Inhibition of CYP3A4	Gefitinib	Increase the level of gefitinib
	Inhibition of CYP3A4	Etoposide	Expect to increase the etoposide toxicity
	–	Anthracycline	No effect
	Inhibition of CYP3A4	Everolimus	Increase the level of Everolimus

* It should be mentioned that hyperbilirubinemia can be seen with atazanavir, but is not a guidance for chemotherapy drug adjustment dose (Rudek et al., 2011).

plasma protein by rate of 93 % and is mainly excreted in feces (Klotz et al., 1990). Its half-life based on administration route is around 12 – 20 hours (Canga et al., 2008). The absorption, distribution and elimination of ivermectin is dependent on P-glycoprotein, on the other hand, it is a potent inhibitor of P-glycoprotein (Ménez et al., 2012). The main interactions of this drug are caused by its effects on P-glycoprotein. Ivermectin may change the p-glycoprotein ABCB1 substrate (Ménez et al., 2012). The most reported side effects are reported in the context of its use an antiparasitic drug as the result of immunologic response to parasite, including skin rash, fever, headache, nausea and dizziness (Juarez et al., 2018). Drug interaction of Ivermectin and chemotherapy agents is an important issue both in treatment of cancer or COVID-19 (Canga et al., 2008).

There are not enough clinical data about ivermectin drug interactions. It is reasonable to cautiously administer this drug with drugs that are metabolized by CYP3A4 and induce or inhibit P-glycoproteins (Table 3) (Jiang et al., 2019; Mealey et al., 2003).

Table 3
Ivermectin DDIs:

Covid-19 drug	Type of interaction	
Ivermectin	P-glycoprotein substrates	Doxorubicin (Kim, 2002)
		Mitoxantrone (Kim, 2002)
		Paclitaxel (Lin, 2003)
		Vinblastine (Lin, 2003)
		Vincristine (Kim, 2002)
		Ivermectin (Lin, 2003)
		Lapatinib (Cidon, 2017)
		Lenvatinib (Cidon, 2017)
		Sorafenib (Cidon, 2017)
		Actinomycine D (Zhou, 2008)
		Docetaxel (Zhou, 2008)
		Imatinib (Zhou, 2008)
		Irinotecan (Zhou, 2008)
		Mitomycine C (Zhou, 2008)
		Topotecan (Zhou, 2008)
	P-glycoprotein inhibitors	Etoposide (Kim, 2002)
		Tamoxifen (Kim, 2002)
		Ivermectin (Ménez et al., 2012)
		Methadone (Kim, 2002)
		Vinblastin (Zhou, 2008)
	P-glycoprotein inducers	Cisplatin (Zhou, 2008)
		Daunorubicin (Zhou, 2008)
		Doxorubicin (Zhou, 2008)
		Vinblastine (Zhou, 2008)
		Vincristine (Zhou, 2008)
		Etoposide (Zhou, 2008)

3.5. Remdesivir

Remdisivir (RDV) is a new investigational antiviral agent, that have been used against coronavirus. RDV inhibits the RNA-dependent RNA polymerase (Al-Tawfiq et al., 2020; Gordon et al., 2020; Tchesnokov et al., 2019).

Its oral bioavailability is very low, so it is used intravenously (Mealey et al., 2003). Unfortunately, there are not any data about the drug pharmacokinetic and drug-drug interaction. In a phase II trial on remdesivir, 9 cases of side-effects were reported but 8 cases of them were not related to remdesivir (Tchesnokov et al., 2019).

While waiting for more definite evidence, physicians should prescribe this drug with caution in cases of multiple medications.

3.6. Tocilizumab

Tocilizumab (TCZ, Actemra) is an Ig G recombinant humanized monoclonal antibody that blocks the receptor of IL-6. TCZ has been used for treatment of rheumatoid arthritis (Zhang and Brennan, 2010). As the result of the cytokine storm the increased level of IL-6 is observed in the course of COVID-19, based on this finding, TCZ is currently used for treatment of this condition (Coomes and Haghbayan, 2020).

There is no information regarding the metabolism and plasma protein binding of tocilizumab. Its half- life depending on administration dose and routes is 11–13 days (Grange et al., 2011).

Reported adverse effects are upper respiratory tract infection, neutropenia, headache, hypertension, ALT elevation and lipid profile changes. Mild reaction in infusion site is common (Oldfield et al., 2009; Sheppard et al., 2017). One study showed that TCZ has no effect on QT interval (Grange et al., 2011).

Among the drugs that has concurrently used with TCZ, It seems that co-administration of TCZ has no effect on MTX pharmacokinetic (Schmitt et al., 2012). Increasing the level of IL-6 is the consequence of blocking IL-6 receptors by TCZ. Elevated IL-6 reduces CYP450 activity, TCZ may reverse this reduced activity of CYPA50. This issue must be kept in mind when we want to administer TCZ with other agents that metabolized by CYP450 (Schmitt et al., 2011). TCZ is an immunosuppressive agent; therefore, there is a concern toward its administration in cancer patients who are already immunosuppressed as the result of chemotherapy. It should also be noted that due to the long half-life of TCZ monitoring of this interaction may be necessary for 1–2 months after the discontinuation of TCZ (Roche Pharma, 2013).

4. Conclusion

In conclusion, there are limited data about the metabolism or drug

interactions some of the current COVID-19 treatments. But some of them have been studied more. Knowing of the metabolism, half-life and drug interactions of the current covid-19 treatments help physicians to make a better and quick decisions and manage correctly.

Declaration of Competing Interest

There are no conflict of interest.

CRediT authorship contribution statement

Anya Jafari: Data curation, Writing - original draft. **Sahar Dadkhahfar:** Writing - review & editing. **Sahra Perseh:** Data curation.

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