Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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REVIEW ARTICLE

Potential Drug Interactions of Repurposed COVID-19 Drugs with Lung Cancer Pharmacotherapies

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Lung cancer patients are at heightened risk for developing COVID-19 infection as well as complications due to multiple risk factors such as underlying malignancy, anti-cancer treatment induced immunosuppression, additional comorbidities and history of smoking. Recent literatures have reported a significant proportion of lung cancer patients coinfected with COVID-19. Chloroquine, hydroxychloroquine, lopinavir/ritonavir, ribavirin, oseltamivir, remdesivir, favipiravir, and umifenovir represent the major repurposed drugs used as potential experimental agents for COVID-19 whereas azithromycin, dexamethasone, tocilizumab, sarilumab, famotidine and ceftriaxone are some of the supporting agents that are under investigation for COVID-19 management. The rationale of this review is to identify potential drug-drug interactions (DDIs) occurring in lung cancer patients receiving lung cancer medications and repurposed COVID-19 drugs using Micromedex and additional literatures. This review has identified several potential DDIs that could occur with the concomitant treatments of COVID-19 repurposed drugs and lung cancer medications. This information may be utilized by the healthcare professionals for screening and identifying potential DDIs with adverse outcomes, based on their severity and documentation levels and consequently design prophylactic and management strategies for their prevention. Identification, reporting and management of DDIs and dissemination of related information should be a major consideration in the delivery of lung cancer care during this ongoing COVID-19 pandemic for better patient outcomes and updating guidelines for safer prescribing practices in this coinfected condition.

Key Words: Drug-drug interactions, COVID-19, Lung cancer, QT prolongation, Tyrosine kinase inhibitors, Chemotherapy.

Introduction

The coronavirus disease-19 (COVID-19) or novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has adversely affected the global healthcare system, particularly oncology care. Malignancy and anti-cancer medications such as chemotherapy and radiotherapy can lead to an immunosuppressive state in cancer patients (1,2). Therefore, cancer patients have a heightened risk of developing COVID-19 infection. Recent literatures have reported that lung cancer patients are more susceptible to COVID-19 infection (3,4). Smoking is also associated with a high risk of developing COVID-19 severity among lung cancer patients (5). Limited literatures are available on the incidence/prevalence of COVID-19 infection among lung cancer patients. A nationwide analysis of cancer among 1590 COVID-19 patients from 575 hospitals in 31 provincial regions of China has revealed that 18 cases (1%) had a history of cancer. Lung cancer was the most common type of cancer accounting for 28% (5 cases) of the cancer cases (3). Other studies from Wuhan, China has also revealed that lung cancer was the most common type of cancer in COVID-19 patients (6,7). Results from electronic medical records (EMR) analysis of Mount Sinai Health System (MSHS) on COVID-19 patients in New York City has revealed that 6% of patients (n = 334) had cancer. Among these cancer patients, 6.8% (n = 23) had lung cancer, which was the third highest cancer after breast and prostate cancers (8).

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Lung cancer treatment includes long term chemotherapy cycles and drug treatments which upon co-administration with repurposed COVID-19 drugs and other supporting agents used for COVID-19 management could increase the risk for DDIs. DDIs possess significant detrimental effects on patient safety, health economics, and treatment outcomes particularly in patients on polypharmacy (9−13). A large number of current drugs used in the market for a long period are being tried globally as experimental targets and as supportive care therapies for COVID-19 management since repurposing old drugs offers the advantage of not needing to go through the rigorous procedures of developing a new chemical entity and further drug approval process. However, the results of different trials/studies conducted in different countries have yielded conflicting reports on safety and efficacy issues at various stages and in a different population (14−20). Chloroquine, hydroxychloroquine (HCQ), lopinavir/ritonavir, ribavirin, oseltamivir, remdesivir, favipiravir, and umifenovir are the major COVID-19 repurposed drugs whereas azithromycin, dexamethasone, tocilizumab, sarilumab, famotidine and ceftriaxone are some of the supporting agents that are currently employed as potential experimental targets for COVID-19 treatment (21−27).

There is only sparse information available regarding COVID-19 treatment outcomes in lung cancer patients. Recently, Jacobo R et al. reported 17 cases of lung cancer with COVID-19 infection among 45 cancer patients (37.7%). Among these 17 patients, 8 (47.1%), 2 (11.7%), 1 (5.9%), and 1 (5.9%) patient received hydroxychloroquine+ azithromycin, lopinavir/ritonavir + hydroxychloroquine, lopinavir/ritonavir + hydroxychloroquine + azithromycin, and hydroxychloroquine treatments, respectively. The treatment with hydroxychloroquine and azithromycin combination was found to improve the outcome of lung cancer patients with COVID-19, with only 1 death being reported for this treatment (OR 0.04, CI 0.01−0.57, $p = 0.018$) (28). Luo J et al. reported that 62% and 25% of the lung cancer patients coinfected with COVID-19 (n = 102) were hospitalised and died respectively. Among the hospitalized patients, hydroxychloroquine treatment (73%, $n = 35/48$) was not associated with improved COVID-19 outcomes (OR for ICU/intubation/DNI 1.39, 95% CI 0.37−4.56, $p = 0.7$, and OR death 1.03, 95% CI 0.26−3.55, $p = 0.99$) (29). Considering the risk factors and reported incidence/prevalence pattern, a larger population of lung cancer patients could be anticipated to be infected with COVID-19 infection in the coming days. Therefore, assessment of potential DDIs occurring with the lung cancer medications with the repurposed COVID-19 drugs can provide preliminary knowledge for screening, identification, and management of DDIs in this coinfected condition. In this scenario, we assessed the potential DDIs between the repurposed COVID-19 drugs and lung cancer pharmacotherapies using the drug interaction checker of IBM Micromedex®.

Methods

We conducted a search for potential DDIs between lung cancer medications and repurposed COVID-19 drugs using the drug interaction checker of IBM Micromedex® (30). Drugs used in the treatment of lung cancer were compiled from the National Comprehensive Cancer Network (NCCN) Guidelines® and Food and Drug Administration (FDA) approved lung cancer drugs (31−33). The repurposed COVID-19 drugs and supporting agents were compiled from several guidelines and literature search till October 21st 2020 (34−39). The interaction tool in Micromedex provides instant access to DDIs. COVID-19 repurposed drugs and lung cancer medications were selected from the search field and added to the 'drugs to check' in the interaction tool. Information on DDIs was manually extracted using Micromedex. Micromedex classifies the severity of DDIs as contraindicated, major, moderate, minor, and unknown. Additionally, Micromedex provides description of all DDIs and clinical management information for certain cases. A total of 61 potential DDIs along with their severity was identified from Micromedex. Additionally, relevant literatures were extracted from PubMed and Google Scholar for gathering information on the mechanism of interaction, clinical consequences, monitoring parameters, and precautions for the DDIs found from the drug interaction checker of Micromedex. We excluded non-scientific commentaries from our review. Only English literatures were included in the review. No DDI data were available for ribavirin, oseltamivir, remdesivir, tocilizumab, sarilumab, and ceftriaxone with lung cancer medications using the Micromedex interaction tool. Favipiravir and umifenovir were not found in the search list of Micromedex interaction tool till 21st October 2020. The severity grading of DDIs (Figure 1) was based solely on the results of the drug interaction checker of Micromedex. Micromedex provides a more reliable database for the severity grading of DDIs (40).

Mechanism of Drug Interactions of Repurposed COVID-19 Drugs with Lung Cancer Pharmacotherapies

Pharmacodynamic Interactions

Pharmacodynamic interactions occur when both drugs affect similar molecular targets or the same physiologic pathways leads to altered efficacy and toxicity. It can be additive, synergistic, or antagonistic (41).

QT Prolongation

As chloroquine, hydroxychloroquine, lopinavir, ritonavir, azithromycin, and famotidine are associated with QT prolongation, sweeping usage of these drugs along with insufficient consideration for concomitant use of other QT

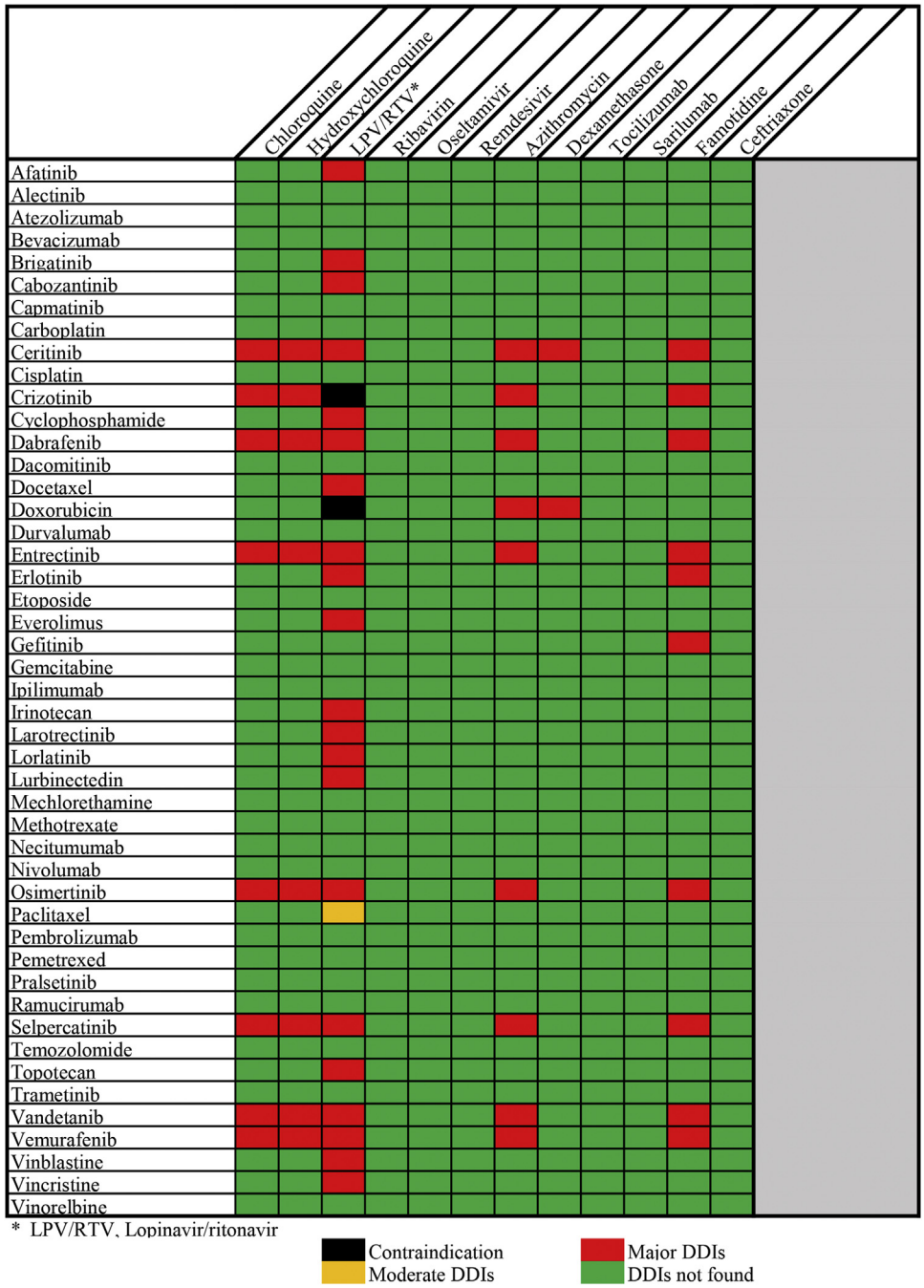

Figure 1. Drug-drug interactions severity chart.

prolonging agents could result in an increased frequency of cardiovascular adverse events (42–46). Further, there is a high prevalence of COVID-19 infection among patients with underlying cardiovascular diseases and COVID-19 infection can also provoke myocardial injury (47). Chloroquine and HCQ are both 4-aminoquinoline agents historically used for malaria (48). Recently these drugs have gained significant attention for their exploratory investigation for COVID-19 treatment (44,49–52). Chloroquine and HCQ are known to cause cardiotoxicity and QT prolongation (42,53–56). Lopinavir/ritonavir are human immunodeficiency virus (HIV) protease inhibitors that are under clinical investigation for COVID-19 infection. Evidences have demonstrated their activity against COVID-19 via inhibition of 3-chymotrypsin-like protease (17,21,57,58). Lopinavir/ritonavir are also associated with

a potential for causing QT prolongation (57,59). The addition of azithromycin to hydroxychloroquine resulted in superior viral clearance compared to hydroxychloroquine alone in COVID-19 patients (60). However, azithromycin exposure has been reported to cause ventricular arrhythmia, torsades de pointes and sudden cardiac arrest and the FDA has added the related warning information to the package inserts (46,61). Therefore, a careful electrocardiogram (ECG) assessment is advised during azithromycin usage for identifying any signs of QT prolongation (21,46). Concomitant use of azithromycin with hydroxychloroquine can cause a greater change in the QTc prolongation than HCQ alone (44). Reports of favipiravir induced QT prolongation are conflicting (62,63). Invitro reports showed that remdesivir weakly inhibited hERG channel (IC50 value for the inhibitory effect was 28.9 μM), suggesting a potential for probable QT prolongation (64). Famotidine, a histamine-2 receptor antagonist, has been recently considered to be a potential repurposed COVID-19 drug as it has been reported to decrease the composite outcome of death intubation in COVID-19 patients (27). Studies have reported that famotidine administration was associated with prolonged QT interval (65,66).

Multikinase inhibitors (MKIs) such as tyrosine kinase inhibitors (TKIs) are commonly used in the management of lung malignancy, particularly in non-small cell lung cancer (NSCLC) (41). QT prolongation is one of the major known adverse effects of TKIs (67). Approximately 4% of patients receiving TKIs are associated with QT prolongation (68). QT prolongation is one of the most serious toxicities associated with crizotinib and ceritinib, that are FDA approved for ALK (anaplastic lymphoma kinase) positive NSCLC patients (67,69,70). 4% of patients receiving osimertinib, an approved drug for EGFR (epidermal growth factor receptor) T790M mutated NSCLC patients developed QT prolongation (68,71,72). Dabrafenib, which is an approved BRAF (B-Raf proto-oncogene) inhibitor along with entrectinib, an inhibitor of the tyrosine kinases ALK, TRKA/B/C (tropomyosin receptor kinase) and ROS1 (c-ros oncogene1) were reported to cause QT prolongation (73,74). Vandetanib, vemurafenib and selpercatinib were also reported to cause QT prolongation as one of the major adverse effects (75−77). Co-administration with COVID-19 repurposed drugs with these lung cancer medications can lead to additive effects on QT interval prolongation which may further increase the risk of cardiac arrhythmias and torsades de pointes (78). Careful monitoring, dosage adjustment, withhold/withdrawal of drugs, and/or avoidance of drugs may be required if concomitant medications with the risk of QT prolongation are taken by patients (49,79). Therefore, optimal medication surveillance and regular ECG to monitoring for QT interval prolongation is advised in COVID-19 patients undergoing chemotherapy for lung cancer.

Pharmacokinetic Interactions

Pharmacokinetic interactions occur when one drug influences other drug's absorption, metabolism, distribution, and elimination. Cytochrome P450 (CYP) and its isoenzymes are responsible for most of the drug metabolism and pharmacokinetic DDIs due to altered plasma concentrations (41).

Drug Absorption

Gastrointestinal pH is the most important factor affecting the solubility and exposure of drugs particularly of TKIs such as erlotinib, gefitinib, and selpercatinib. Concomitant administration of histamine H2-receptor antagonists like famotidine may increase stomach pH that can reduce TKI solubility, absorption, and bioavailability. Therefore, the potential for such interactions is clinically important, and apt drug administration time interval management is required (77,80−82).

Drug Metabolism

Chloroquine and hydroxychloroquine are metabolized into active metabolites in the liver through the N-desethylation pathway mediated by CYP2D6, CYP3A4, CYP3A5, and CYP2C8 enzymes (83−87). Lopinavir undergoes metabolism by CYP3A4 enzymes in both the intestine and the liver and acts as a substrate for P-glycoprotein (P-gp) transporter (88,89). Lopinavir/ritonavir is a strong CYP3A inhibitor and hence can increase the exposure of brigatinib (90). A 50% dose reduction of brigatinib is suggested if concomitant use with strong CYP3A inhibitors is unavoidable (90). Similarly, concomitant use of lopinavir/ritonavir with lung cancer medications like crizotinib and dabrafenib can also increase the plasma concentration of the latter and consequently lead to adverse reactions (73,91). Ritonavir is a very potent inhibitor of CYP3A4 enzyme and hence can increase the plasma concentration of lung cancer medications like ceritinib, everolimus, docetaxel, doxorubicin, entrectinib, and erlotinib that are majorly metabolized by CYP3A4 (41,92−100). Ritonavir may increase lorlatinib and paclitaxel plasma levels due to inhibition of CYP3A-mediated metabolism (101,102). Azithromycin has been shown to be a weak CYP3A4 substrate with no significant ability to induce nor inhibit CYP3A4 activity or organic anion transporting polypeptide (OATP1B1) activity (103−105).

Dexamethasone is a widely used first-line agent for the prevention and management of chemotherapy induced nausea and vomiting (106). Dexamethasone is a potent steroid and also an inducer of CYP3A4 (107,108). Therefore, concomitant use with ceritinib (a strong CYP3A inhibitor) should be avoided and close monitoring of side effects is recommended (41). Larotrectinib, cabozantinib, irinotecan,

cyclophosphamide, topotecan, and lurbinectedin are metabolized primarily via CYP3A4. Therefore, caution is required when these drugs are used concomitantly with lopinavir or ritonavir and monitor for possible changes in the efficacy or toxicity profile (109,110). Vincristine and vinblastine are CYP3A4 and P-gp substrates. The plasma concentrations of vincristine and vinblastine are likely to be increased when concomitantly administered with protease inhibitors (109,111).

Remdesivir is a novel adenosine analogue therapeutically used for RNA based viruses including the Ebola virus (EBOV) and the *Coronaviridae* family viruses (24). Remdesivir is an inhibitor of CYP3A4, multidrug resistance-associated protein 4 (MRP4), bile acid export pump (BSEP), OATP1B1, OATP1B3, and sodium-taurocholate cotransporter protein (NTCP) *in vitro* (64). The plasma concentrations of remdesivir may increase with the concomitant use of strong CYP enzyme or P-gp inducers (112). Favipiravir is a purine nucleic acid analogue which undergoes ribosylation and phosphorylation into an active metabolite favipiravir ibofuranosyl-5′-triphos-phate (T-705RTP) intracellularly (113). T-705RTP interferes with the viral replication process by inhibiting the RNA-dependent RNA polymerase (114). Tocilizumab is an interleukin 6 (IL-6) receptor antagonist (115). Early study reports suggest that COVID-19 patients with multiple comorbidities who received tocilizumab had an improved outcome (116,117). Sarilumab is another IL 6 receptor antagonist that is being trialed in a double-blind study (118). Up-regulation of IL-6 reduces the activity of CYP450 enzymes, and blockade of this cytokine may improve CYP function. This may lead to decreased bioavailability of drugs metabolized by CYP enzyme.

As CYP3A4 is responsible for the majority of drug metabolism, it is likely to decrease the bioavailability of other drugs when co-administered with tocilizumab. Thus, caution is required when co-prescribing tocilizumab and CYP-metabolized drugs (119).

Drug Transportation

Drug interactions concerning drug transportation (efflux and uptake) have significant clinical relevance during the administration of TKIs (41). Efflux drug transporters like P-gp belonging to ATP-binding cassette subfamily B member 1 and breast cancer resistance protein (BCRP) plays a crucial role in the occurrence of DDIs (41). The plasma concentration of afatinib (P-gp and BCRP substrate) is increased when it is co-administered with ritonavir which is a strong P-gp and BCRP inhibitor. Therefore, monitoring of adverse effects and staggered dosing, 6 h or 12 h apart from afatinib is recommended in this scenario (41,120). Ritonavir may increase the intracellular accumulation of doxorubicin, a P-gp substrate leading to the systemic toxicity of the latter (97,98). The DDIs of experimental COVID-19 repurposed drugs and supporting agents with various lung cancer medications are shown in Supplementary Table 1 and the severity of DDIs is shown in Figure 1.

Drug Interactions of Repurposed Drugs for COVID-19 with Lung Cancer Supportive Care Pharmacotherapies

In addition to lung cancer medications, several drugs are given as supportive care for lung cancer patients (121). Supportive care drugs are usually used for the treatment of side effects, tumor symptoms, and concomitant diseases. A significant proportion of the patients assumed three or more different drugs in addition to chemotherapy in advanced stages of NSCLC (121). Therefore, we have overviewed potential drug interactions caused by repurposed COVID-19 drugs and some of the major supportive care drugs recommended by NCCN guidelines using the drug interaction checker of IBM Micromedex®. Cancer supportive care drugs were compiled from NCCN recommendations of drugs for adult cancer pain, haemopoietic growth factors, cancer, and chemotherapy induced anemia, distress management, cancer related fatigue, cancer associated venous thromboembolic disease, emesis, immunotherapy related toxicities, and palliative care (122). Methadone is an opioid drug used for cancer pain which is associated with QT prolongation (123). Similarly, antiemesis drugs such as olanzapine, dolasetron, granisetron, ondansetron, and prochlorperazine are also associated with QT prolongation (124−127). Antipsychotic drugs used in cancer palliative care such as haloperidol, quetiapine, and risperidone may cause prolonged QT interval, serious cardiovascular side effects, and can leads to torsades de pointes and death (124). Other supportive care drugs such as donepezil, octreotide, and metronidazole are also reported to cause QT prolongation (128−130). Therefore, concomitant use of these supportive care drugs with chloroquine, hydroxychloroquine, lopinavir, ritonavir, azithromycin, and famotidine could result in a potential interaction and an increased frequency of cardiovascular adverse events. Commonly used drugs for cancer pain such as codeine, fentanyl, lidocaine, oxycodone, hydrocodone, and tramadol are majorly metabolized by CYP3A4 (131). CYP3A4 has been considered as a significant enzyme for the metabolism of other supportive care drugs such as midazolam, naloxegol, quetiapine, and zolpidem (132−135). Therefore, concomitant use of these drugs with strong CYP3A inhibitors such as lopinavir and ritonavir may increase the exposure and risk of adverse effects. Administration of ritonavir along with oral prednisolone may increase systemic corticosteroid exposure and may result in the development of Cushing syndrome (136). Concomitant use of morphine and ritonavir may increase the exposure of morphine and increase the risk of adverse effects (131). Therefore, it is important to

recognize potential drug interactions between cancer supportive care drugs and repurposed COVID-19 drugs.

Conclusion

There is a high potential for the occurrence of major DDIs associated with the concomitant use of COVID-19 repurposed treatments with lung cancer medications, with QT prolongation being the most commonly identified DDI. This review is intended to provide an alert for clinicians and pharmacists for developing holistic scientifically interrogative strategies for screening, identification, reporting, and management of potential DDIs in lung cancer patients coinfected with COVID-19 infection. Currently, there is limited data available regarding the DDI profile of certain lung cancer medications with repurposed drugs for COVID-19. Hence, further scientific reports from clinical trials and observational studies are required to provide more concrete data on prevalence, risk factors, severity assessments and clinical management strategies of DDIs between lung cancer medications and repurposed drugs for COVID-19 during this pandemic.

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Conflicts of Interest

The authors declare no conflict of interest.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.arcmed.2020.11.006.

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