Men's Health Journal. 2023; 7(1): e1

OPEN ACCESS

REVIEW ARTICLE

Chemoimmunotherapy Drugs with Antiviral Activity to Treat Patients with Lung Cancer and COVID-19; a Narrative Review

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Received: March 2023; Accepted: April 2023; Published online: May 2023

Abstract: Every year lung cancer is a cause of high morbidity and mortality in the human population. However, since 31 December 2019, the coronavirus disease 2019 [COVID-19] had importantly affected various degrees of pulmonary regions. Therefore, patients with lung cancer must be the priority group for COVID-19 prevention, treatment, and vaccination during the COVID-19 pandemic. Until now, clinicians and patients know that most individuals with respiratory distress and/or those with a weakened immune system are more susceptible to COVID-19, however, the associations with lung cancer remain unclear. Here, we present the combination of common chemotherapeutic drugs with a historical antiviral activity that may be too immunosuppressive to eliminate COVID-19-infected cells in patients with lung cancer. This review will help understand the preferred chemoimmunotherapy drugs for severe forms of COVID-19 [SARS-CoV-2] in these patients.

Keywords: COVID-19, Antiviral activity, Chemotherapeutic drugs, Lung cancer

Cite this article as: Olfati A, Soufivand P, Saadatfar A. Chemoimmunotherapy Drugs with Antiviral Activity to Treat Patients with Lung Cancer and COVID-19; a Narrative Review. Mens Health J. 2023; 7(1): e1.

1. Introduction

According to the last update of the National Center for Immunization and Respiratory Diseases (NCIRD) on 15 February 2020, six types of coronaviruses were known to infect the human's population, as follows: 1) 229E (α-coronavirus), 2) NL63 (α-coronavirus), 3) OC43 (β-coronavirus), 4) HKU1 (β-coronavirus), 5) MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome), 6) SARS-CoV-1 (the beta coronavirus that causes severe acute respiratory syndrome).
Coronaviruses are distributed broadly among animals and humans and cause multi-organ failure, especially in various degrees of pulmonary regions.
Like the other coronaviruses, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily causes respiratory tract infections (1). The novel coronavirus and SARS have 96% genomic similarity and because of this, special types of symptoms are seen in both of them. Two types of the mentioned coronaviruses include SARS-CoV and MERS-CoV responsible for the 2019 coronavirus disease (COVID-19) pandemic in Wuhan (Hubei Province, China) since 31 December 2019 by entry into human cells, its remarkably sophisticated gene expression, and replication-transcription complex, its extensive remodeling of the intracellular environment, and its multifaceted immune evasion strategies (2). Subsequently, this illness changed into an epidemic all over the world.
During the panic-stricken emergency, cancer patients show deteriorating conditions and poor outcomes from the COVID-19 infection (1), and the main dysfunction of coronavirus infection is damage to the alveolar and acute respiratory failure (3), which causes great epidemic concerns. Recent studies demonstrated that lung cancer was the most frequent type among patients with COVID-19 (4).
On the other hand, lung cancer is known as one of the major causes of cancer-related mortality worldwide. Thus, such patients could be at the greatest risk due to the nosocomial

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spread and systemic immunosuppressive caused by the malignancy and anticancer treatments. These individuals are more vulnerable to infection by COVID-19 infection than healthy people (5, 6), with higher rates of hospitalization and death (4, 7), due to acute respiratory failure and systemic coagulopathy [8]. COVID-19 led to death in approximately 25% of patients with lung cancer. Luo et al. [9] found that COVID-19 was severe in patients with lung cancer (62% hospitalized, 25% died). All this confirms the increased risk for cancer patients, especially those with lung cancer during this challenging time.

With the rapid worldwide spread of COVID-19, advanced treatment for patients with lung cancer was highly recommended.

Effective therapy is thus urgently needed. In this review, the authors sought to specify the efficacy and safety of common chemotherapeutic drugs with historical antiviral activity (chemoimmunotherapy) of COVID-19 in the treatment of patients with lung cancer.

1.1. Screening and chemoimmunotherapy

So far, there are no definitive treatments for COVID-19, and the treatments available today are based on previous experience with similar viruses such as SARS-CoV, MERS-CoV, and Influenza virus (10). Large randomized controlled trials (RCTs) stand as the Gold Standards for COVID-19 therapy and offer a solid scientific base on which to make treatment decisions (11).

It is recommended that cancer patients receiving antitumor treatments should have vigorous screening for COVID-19 infection and should avoid treatments causing immunosuppression or have their dosages decreased in case of COVID-19 infection (1). The major adverse effects of chemotherapeutic agents also referred to as antineoplastic agents, are associated with off-target genotoxicity, dose-dependent myelosuppression, and risks of secondary cancer (12). During this challenging time for reducing mortality and morbidity rates, Loscocco [13] suggested that such patients should be screened both for a hyperinflammatory state using laboratory tests [e.g. ferritin, decreased platelet count, or erythrocyte sedimentation rate] and for H-score to identify the subgroup of patients for whom immunomodulating/immunosuppressive therapies as steroids, immunoglobulin, cytokine blockers, and Janus kinase inhibitors could improve survival. And, understanding the patient-specific (like smoking history, hypertension, age, and chronic obstructive pulmonary disease) and cancer-specific features (like prior thoracic surgery/radiation and recent systemic therapies) that impact the severity of COVID-19 could inform optimal cancer care during this outbreak (9).

Since vaccines are still at least 12–18 months away, the focus is on drug development by exploring the available therapeutic possibilities. One of the main strategies for improved immunotherapy drugs is to increase levels of endogenous reactive metabolites (such as reactive oxygen species (ROS)) for selective toxicity to SARS-CoV-2 by preferential damage to the viral proteome (14).

Numerous clinical and laboratory findings showed that immunotherapy can act as a double-edged sword. On the one hand, patients undergoing immunotherapy might be more immunocompetent than those receiving chemotherapy and, therefore, have a lower risk of developing COVID-19-related complications. On the other hand, ICI-related immune hyper-activation could promote the onset of a “cytokine storm syndrome (CSS) (15). Meanwhile, in recent days mortality in COVID-19 is primarily created with a CSS, resulting in a state of hyperinflammation syndrome and multiorgan failure (16). Thus, more understanding about the preferred chemoimmunotherapy drugs for severe forms of COVID-19 is urgently needed in patients with lung cancer.

1.2. Tocilizumab

Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the interleukins-6 (IL-6) receptor in patients with lung cancer.

IL-6 has been associated with a worse prognosis (16, 17). National Institutes of Health on March 5, 2021, hypothesized that modulating the levels of pro-inflammatory IL-6 or its effects may reduce the duration and/or severity of COVID-19 illness. The rate of the severity of the disease depends on the viral load. By blocking the IL-6 receptor, TCZ can disrupt this cascade of events and restore the functionality of the alveoli in a patient with none small-cell lung cancer (NSCLC) treated with chemoimmunotherapy (18). Ascierto (19) reported improved clinical, biological, and radiological features as soon as 5 days after TCZ treatment in patients with COVID-19 with a risk of CSS confirming the safety and efficacy of TCZ. The results from other observational studies have shown that the clinical outcome for patients with NSCLC undergoing chemoimmunotherapy for stage IV lung adenocarcinoma with TCZ can be safely used to treat COVID-19 pneumonia (18). In patients with COVID-19 pneumonia and respiratory failure requiring ventilatory support, treatment with TCZ was associated with a clinical benefit (rapid and sustained) for more than 75% of the patients [20]. Some of the main reasons for the suitability of TCZ in critical patients (like rheumatoid arthritis and cytokine release syndrome) include the low risk of immunogenicity, the flexibility of intravenous and subcutaneous administration, and the convenience of the once-weekly, self-administered, SC regimen (21).

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1.3. Etoposide

Etoposide is a chemotherapeutic drug widely used for the therapy of several types of cancer, such as leukemia, lymphoma, and small cell lung cancer (an aggressive disease with poor prognosis), and promotes apoptosis of cancer cells by inhibiting the topoisomerase II enzyme (12). The administration of up to five doses of low-dose etoposide therapy to an adult, costs approximately $80 (as of April 21, 2020) (12). Oral etoposide administration exhibits advantages for the quality of life of the patient as well as economic benefits (22).

Moreover, low-doses of this chemotherapeutic drug could improve acute respiratory distress syndrome (ARDS), pulmonary edema, and other fatal comorbidities by suppressing the intrapulmonary recruitment and activation of macrophages (23). ARDS is associated with an overproduction of cytokines (IL-6, IL1, IL-8, IL-12, CCL-2, and TNFα) that cause alveolar and vascular lung damage (11). All of this approves low-dose etoposide as the most promising and available anti-inflammation therapy that could improve CSS in patients with viral infections such as SARS-CoV-2 infection and prevents deadly deterioration.

1.4. Gemcitabine

Gemcitabine is a pyrimidine nucleoside analog approved by the Food and Drug Administration for the treatment of various solid cancers, including NSCLC, pancreatic, bladder, and breast cancer (24). Gemcitabine has an antiviral inhibitory effect against 3 types of coronaviruses known to infect humans including MERS-CoV (25), SARS-CoV (25), and SARS-CoV-2 (26). Additionally, gemcitabine could efficiently inhibit SARS-CoV-2 in Huh-7 cells, indicating that their antiviral activities were not cell-type dependent. Although this compound exhibited a dose-dependent inhibition of 2019-CoV replication in infected cells as chloroquine (26). This compound may inhibit SARS-CoV-2 replication by targeting the salvage pathway of pyrimidine biosynthesis and stimulating innate immunity, the same mechanism as the enterovirus (27). By acting as a potent antimetabolite, it inhibits two cellular processes that are both required for DNA biosynthesis, i.e., replicative DNA chain elongation and nucleotide reduction (28).

1.5. Paclitaxel

Paclitaxel (PTX) is known as a representative chemotherapeutic agent with historical antiviral activity for cancer chemotherapy, which induces apoptosis by activating multiple apoptotic markers (like caspase-3 and generation of N-terminal fragment) (29). In patients with previously untreated metastatic squamous NSCLC addition of PTX to the chemotherapy regimen improved overall survival, progression-free survival, and objective response rate, with little impact on severe toxicity (30). The mechanisms of PTX action are associated with enhancing the polymerization of tubulin to stable microtubules and also interact directly with microtubules, stabilizing them against depolymerization by cold and calcium, which readily depolymerize normal microtubules (31). Recently, Al-Motawa et al. (14) provided evidence of the potential vulnerability of SARS-CoV-2 to inactivation by reactive glycating agent methylglyoxal (MG, one of the main endogenous reactive metabolites) and a scientific rationale for the repurposing of PTX for the treatment of SARS-CoV-2 viral inflammation. Increased MG concentration induced by PTX is linked to increased glucose metabolism and related increased formation of MG as a byproduct of glycolysis, providing efficacy and adequate therapeutic index may be established and further studies in vivo are warranted.

1.6. Dexamethasone

Dexamethasone is a glucocorticoid medication commonly used for relieving inflammation in various parts of the body and antiemetic prophylaxis with systemic therapy for cancer (32). Anti-inflammatory drugs including corticosteroids can be used to effectively diminish the effect of CSS and lung damage (33).

Dexamethasone is associated with an increased risk of viral and respiratory infections by reducing the immune response, and causes lymphopenia, which is associated with worse outcomes during COVID-19 infections (32) or the occurrence of secondary infections (11). On June 16, 2020, henceforth, the Guidelines published by the U.K. National Health Service have already announced that the standard of care for patients with COVID-19 will now include dexamethasone (34). Growing evidence suggests that clinicians should prescribe the minimally effective dose of dexamethasone for antiemetic prophylaxis during the COVID-19 pandemic (32). Some recent RCTs reported that treatment with dexamethasone reduced deaths by 1/3 in COVID-19 patients that were mechanically ventilated, and by 1/5 in patients receiving oxygen only. However, in patients who did not need any breathing support, there was no difference in mortality in those treated with dexamethasone compared to controls (11). In addition, another CoDEX RCTs indicated that the use of intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically considerable increase in the number of ventilator-free days (35).

1.7. Palladium

During recent decades, in the field of pharmaceutical chemistry and catalysis, the subjects of metal-based anticancer chemotherapeutic agents have had numerous positive benefits. Recent evidence suggests that Palladium nanoparticles (PdNPs) can act as both a pro-oxidant and as an antiox-

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idant, due to their unique physical and chemical properties (36). Ari et al. (37) found that PdNPs could selectively induce apoptosis for the treatment of NSCLC that is extremely resistant to conventional therapy through ROS.

Currently, Haribabu et al. (38) reported that via the Michael addition pathway, which was confirmed by spectroscopic studies, could synthesis of PdNPs complexes have antiproliferative effects through ROS-mediated mitochondrial apoptosis and docking with the SARS-CoV-2 virus, due to its promising cytotoxic and apoptotic effect. Future ongoing RCTs, with a fixed design, should focus on the use of metal-based anticancer chemotherapeutics compounds directed to more severe COVID-19-infected cells in lung cancer patients to prevent deadly deterioration, the authors say.

2. Conclusion

To effectively manage patients with lung cancer during the COVID-19 pandemic and reduce mortality and morbidity rates, such patients must be the priority group for COVID-19 prevention, treatment and vaccination.

3. Appendix

3.1. Acknowledgment

The authors gratefully acknowledge all colleagues in the Clinical Research, Development Center, Motazedi Hospital, Kermanshah University of Medical Science, Kermanshah, Iran.

3.2. Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

3.3. Funding support

None.

3.4. Author's contributions

All the authors had the same contribution.

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