IJPSR (2021), Volume 12, Issue 2 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 August 2020; received in revised form, 06 January 2021; accepted, 13 January 2021; published 01 February 2021

IMMUNOSUPPRESSIVE ANTI-CANCER DRUGS MAY INCREASE COVID-19 INFECTION RISKS

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Keywords:

Coronavirus, Cancer, Pandemic, SARS-CoV-2, Chemotherapy, ACE2

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ABSTRACT: There is a new public health crisis threatening the world with the emergence and spread of the 2019 novel coronavirus (2019-nCoV). Coronavirus disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which invades cells through the angiotensin-converting enzyme 2 (ACE2) receptor. SARS-CoV-2 shares 82% genome sequence similarity to SARS-CoV and 50% genome sequence homology to Middle East respiratory syndrome coronavirus (MERS-CoV); all three coronaviruses are known to cause severe respiratory symptoms. Cancer patients are more susceptible to infections than healthy persons because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments, such as chemotherapy or surgery. Therefore, these patients might be at increased risk of COVID-19. The level of ACE2 expression may play a role in the risk of reporting COVID-19 infection and the risk of developing more severe forms of the disease in cancer patients the disease in cancer patients. Treatment is essentially supportive; the role of antiviral agents is yet to be established. Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. As we learn to live amidst the virus, understanding the immunology of the disease can assist in containing the pandemic and in developing vaccines and medicines to prevent and treat individual patients.

INTRODUCTION: Three highly pathogenic human coronaviruses (CoVs) have been identified so far, including MERS-CoV, severe acute respiratory syndrome coronavirus (SARS-CoV), and 2019-nCoV, as previously termed by the World Health Organization (WHO) [1-3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(2).714-26

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(2).714-26

The first infections with SARS- CoV-2, which leads to COVID-19, were reported in Wuhan, China at the end of 2019 [4]. COVID-19 is associated with presentations ranging from asymptomatic infections to severe viral pneumonia, acute respiratory distress syndrome, and death [4]. Since then, the spread of COVID-19 has progressively involved countries outside China, leading the World Health Organization (WHO) to make the assessment that COVID-19 can be characterized as a pandemic [5]. As of 30 March 2020, a total of 638,146 cases and 30,039 confirmed deaths have been reported across >150 countries [6].

Genetic analysis of the full-length genome sequences revealed SARS-CoV-2 to be most closely related to a known bat coronavirus termed BatCoV RaTG13, suggesting bats as the likely origin [7].

This suggested the high possibility of animal-to-human transmission. Therefore, the human-to-human transmission was confirmed in 15 health care workers, who were all infected by one patient with the novel coronavirus infection [8].

Patients with cancer are more susceptible to infection than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments, such as chemotherapy or surgery [9-12]. Therefore, these patients might be at increased risk of COVID-19 and have a poorer prognosis.

Cancer treatment in the era of COVID-19 requires consideration of risks and benefits for patients and staff [13]. Recent data suggest patients who have cancer are at increased risk of infection and serious complications fromCOVID-19 [13].

During this extraordinary time, the oncology community faces unprecedented challenges. According to the American Cancer Society, this year, nearly 5000 new cases of cancer will be diagnosed per day in the United States. Initial reports suggest that COVID-19 can be particularly lethal in patients with cancer. The case fatality rate reached 5.6% among cancer patients compared with 2.3% in the general population [14].

For persons with advanced oncologic disease, the futility of treatment in the context of COVID-19 must be frankly considered and discussed.

Epidemiology of COVID-19: Emerging at the end of 2019, COVID-19has become a public health threat to people all over the world. The lower airway is the primary target of the infection for SARS-CoV-2.

In December 2019, a cluster of severe pneumonia cases of unknown cause was reported in Wuhan, Hubei province, China. The initial cluster was epidemiologically linked to a seafood wholesale market in Wuhan, although many of the initial 41 cases were later reported to have no known exposure to the market [15].

A novel strain of coronavirus belonging to the same family of viruses that cause severe acute respiratory syndrome (SARS) and MERS, as well as the 4 human coronaviruses associated with the common cold, was subsequently isolated from lower respiratory tract samples of 4 cases on 7 January 2020 [16]. However, infection with the virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can be asymptomatic or can result in mild to severe symptomatic disease (COVID-19) [17].

The WHO declared that the SARS-CoV-2 outbreak constituted a global health emergency on January 30, 2020 and more than 80 000 confirmed cases had been reported worldwide as of 28 February 2020 [18-19]. On 31 January 2020, the U.S. Centers for Disease Control and Prevention announced that all citizens returning from Hubei province, China, would be subject to mandatory quarantine for up to 14 days [20]. Moreover, on Feb. 11, the new coronavirus disease (previously referred to as 2019-nCoV) received an official name from the WHO, COVID-19 [21]. The International Committee on Taxonomy of Viruses has proposed SARS-CoV-2as the name of the virus that causes COVID-19 [22].

Knowing that coronaviruses are single-stranded RNA, nonsegmented, enveloped viruses, which cause illness ranging in severity from the common cold to severe and fatal illness. The term coronavirus derives from the Latin word corona, which means crown or halo; that designation arises from the appearance of coronavirus virions viewed by electron microscopy, in which the virus particles display a crown-like fringe typically referred to as spikes.

At a briefing on 17 February WHO's director-general, TedrosAdhanom Ghebreyesus, said that more than 80% of patients with covid-19 have a "mild disease and will recover" and that it is fatal in 2% of reported cases. In comparison, the 2003 outbreak of SARS had a case fatality rate of around 10% (8098 cases and 774 deaths), while MERS killed 34% of people with the illness between 2012 and 2019 (2494 cases and 858 deaths) [23, 24]. And, as of February 20, 2020, a total of 75,761 cases and 2130 deaths had been reported in more than 30 countries [25]. Besides, the US Centers for Disease Control and Prevention (CDC) expressing the view that current global circumstances suggest it is likely

this virus will cause a pandemic [26]. We live in a world that is globally connected, in terms of the movement of people, goods, and food, while even within close-knit communities, such as those currently locked down in Italy and elsewhere, the ideal conditions exist for the virus to spread from person to person.

The WHO, on March 11, 2020, has declared the COVID-19 outbreak a global pandemic [27]. At a news briefing, WHO Director-General, Dr. TedrosAdhanom Ghebreyesus, noted that over the past 2 weeks, the number of cases outside China increased 13-fold and the number of countries with cases increased threefold, pointing to the over 118,000 cases of the coronavirus illness in over 110 countries and territories around the world and the sustained risk of further global spread. Further increases are expected. Note that as of March 12, 2020, there have been a total of more than 130000 laboratory-confirmed cases of COVID-19 globally, including more than 80000 within mainland China. Because of its high infectivity, this virus has managed to supersede severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) in death toll. Severe respiratory distress is usually considered the main cause of coronavirus induced death. According to a recent study of the largest clinical sample in China [28].

According to the WHO, on July 29, 2020 there were 17,000,000 confirmed cases of COVID-19, and 650,000 deaths. Beyond confirmed cases, there are also suspected cases of COVID-19, the definition of which evolves over time and the spread of the epidemic. In addition, the criteria vary from country to country **Fig. 1**.

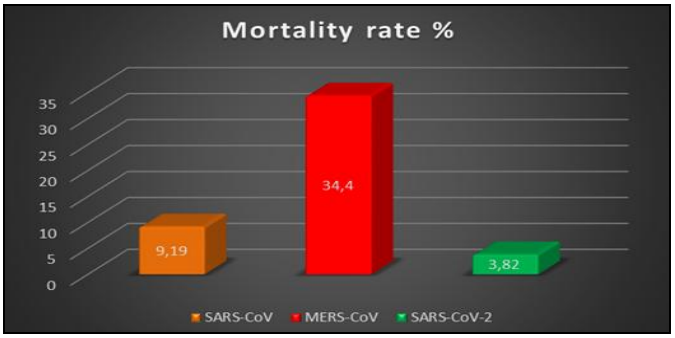

FIG. 1: MORTALITY RATE OF SARS-CoV, MERS-CoV AND SARS-CoV-2

Basic Virology: Coronaviruses are enveloped, positive single-stranded large ribonucleic acid (RNA) viruses that infect humans but also a wide range of animals. Coronaviruses were first described in 1966 by Tyrell and Bynoe, who cultivated the viruses from patients with common colds [29]. Based on their morphology as spherical virions with a core-shell and surface projections resembling a solar corona, they were termed coronaviruses (Latin: corona = crown). Four coronavirus genera, namely alpha-, beta-, gamma- and delta-coronaviruses, exist. While alpha- and beta-coronaviruses apparently originate from mammals, in particular from bats, gamma- and delta-viruses originate from pigs and birds. The genome size varies between 26 kb and 32 kb.

Among the seven subtypes of coronaviruses that can infect humans, the beta-coronaviruses may cause severe disease and fatalities, whereas alpha-coronaviruses cause asymptomatic or mildly symptomatic infections. SARSCoV-2 belongs to the B lineage of the beta-coronaviruses and is closely related to the SARS-CoVvirus [30, 31]. Thus, SARS-CoV-2 is 96% identical at the whole-genome level to a bat coronavirus [31]. The genome of SARS-CoV-2 is similar to that of typical CoVs and contains at least ten open reading frames (ORFs). The first ORFs (ORF1a/b), about two-thirds of viral RNA, are translated into two large polyproteins. In SARS-CoV and MERS-CoV, two polyproteins, pp1a and pp1ab, are processed into 16 non-structural proteins (nsp1-nsp16), which form the viral replicase transcriptase complex [32].

Those nsps rearrange membranes originating from the rough endoplasmic reticulum (RER) into double-membrane vesicles where viral replication and transcription occur [33, 34]. The other ORFs of SARS-CoV-2 on one-third of the genome encodes four structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins [35-37] **Fig. 2**.

Among them, S protein plays the most important role in viral attachment, fusion, and entry, and it serves as a target for the development of antibodies, entry inhibitors, and vaccines [38-40]. The S protein mediates viral entry into host cells by first binding to a host receptor through the receptor-binding domain (RBD) in the S1 subunit and then fusing the viral and host membranes through the S2 subunit [41-43].

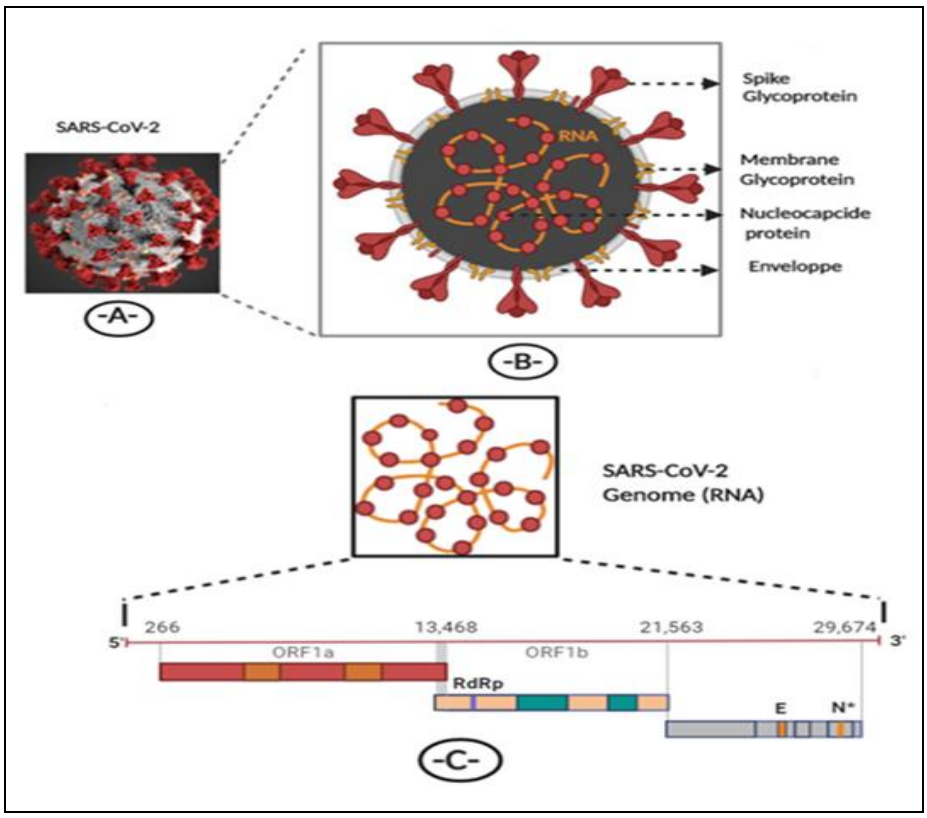

FIG. 2: DEMONSTRATION OF SARS-CoV-2 VIRUS

(A: Representation of the causative virus viewed by electronic microscopy, B: Schematic diagram that shows main constituent of virus, C: Different segments of SARS-CoV-2 genome)

So that a coronavirus can enter and infect a cell, it must recognize a receptor (proteins, lipids, carbohydrates) present at the level of the cell [44]. ACE2 appears to be the gateway to the COVID-19 in the human body and acts as a receptor for COVID-19 [45, 46]. The study performed in vitro experiments, which could confirm that SAR-CoV-2 used ACE2 for cellular entry [47].

Some animal studies have found a positive correlation between the level of ACE2 expression and the risk of declaring COVID-19 infection [48]. Thus, due to the fixation of COVID-19 to ACE2, the virus would cause a decrease in the activity of ACE2, this drop-in activity having been reported as a factor aggravating the inflammatory organ damage induced by COVID-19, in particular pulmonary [49].

An animal study observed a decrease in ACE2 levels in the lungs of mice after administration of SARS-coronavirus, concomitant with worsening of their respiratory functions [45]. So, the level of ACE2 expression may play a role in the risk of reporting COVID-19 infection and the risk of developing a more severe form of the disease.

Similarly, in a recent retrospective study, including 175 Chinese patients infected with COVD-19 and requiring hospitalization, the authors observed that 62% of patients had hypokalemia. The authors explain this hypokalemia by a change in the clearance pathway for angiotensin II with a shift in the ACE1/ACE2 balance (decrease in ACE2 activity caused by COVID-19), in favour from ACE1 favoring aldosterone synthesis and the occurrence of hypokalemia [50].

All in all, it is clear that ACE2 and, in particular, the level of expression of ACE2 seems to play a primordial role in COVID-19 infection. However, its exact role seems complex with potentially a deleterious role during the viral contamination phase since serving as a COVID-19 receptor (and level of severity correlated with the level of expression of ACE2) and both a beneficial role than in the phase of inflammatory tissue damage caused by COVID-19 [51].

Incubation Period and Symptoms of COVID-19: A recent paper provides additional evidence for a median incubation period for COVID-19 of approximately 5 days [52]. However, observations so

far suggest a mean incubation period of five days [53] and a median incubation period of 3 days (range: 0–24 days) [54]. Moreover, WHO reported that the time between symptom onset and death ranged from about 2 weeks to 8 weeks [55].

Nonetheless, the symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days [56]. With significant variation among patients [57]. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days, with a median of 14 days [58]. Thus, this period is dependent on the age of the patient and the status of the patient's immune system. It was shorter among patients >70 years old compared with those under the age of 70 [58].

The most common symptoms at the onset of COVID-2 outbreak are fever, chills, sore throat, dry cough, nausea, vomiting, diarrhea, dyspnoea, lymphopenia, and other signs of upper respiratory tract infections [59-63]. The infection can progress to severe disease with dyspnoea and severe chest symptoms corresponding to pneumonia in approximately 75% of patients [64,] and it may be capable of asymptomatic spread [65, 66]. Afterward, severe cases can lead to cardiac injury, respiratory failure, acute respiratory distress syndrome, and death [67]. The intestinal symptoms were rarely reported in patients with COVID-19 [68-70].

Immunopathology of COVID-19: The immune system is the major protective system of the body against invading foreign bodies and infectious agents [71]. Further, all immune responses are a combination of nonspecific (innate) and specific (adaptive) immunity. During SARS-CoV-2 infection, both innate and adaptative immune cells synergistically participate in the anti-viral response [72].

The pathogenesis of COVID-19 is still under investigation; for most patients, COVID-19 might affect only the lungs because it is mainly a respiratory disease. Thus, the effective antiviral responses of the host innate and adaptive immunity, including the production of various proinflammatory cytokines, the activation of T cells, CD4 and CD8+ T cells, are essential for controlling the viral replication, limiting the spread of virus, inflammation, and cleaning the infected cells [73, 74]. Moreover, cytokine storm (CS) refers to an excessive and uncontrolled release of pro-inflammatory cytokines. CS syndrome can be caused by a variety of diseases, including infectious diseases, rheumatic diseases, and tumor immuno-therapy. Clinically, it commonly presents as systemic inflammation, multiple organ failure, and high inflammatory parameters. Note that in infectious diseases, CS usually originates from the focal infected area, spreading all over the body through circulation. In coronavirus pneumonia, such as SARS and MERS, accompanied by rapid virus replication, a large number of inflammatory cell infiltration and CS, this last can initiate viral sepsis and inflammatory- induced lung injury which lead to other complications including pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, shock, organ failure and potentially death [75, 76].

A recent study reported that the activation of complement as an integral component of the innate immune response to viruses with its component C3 exacerbates disease in SARS-CoV and that C3-deficient mice infected with SARS- CoV exhibited less respiratory dysfunction [77]. The N proteins of SARS-CoV, MERS-CoV, and SARS-CoV-2 were found to bind to MASP-2, the key serine protease in the lectin pathway of complement activation, resulting in aberrant complement activation and aggravated inflammatory lung injury [78]. The tissue injury caused by the virus could induce the exaggerated production of proinflammatory cytokines, the recruitment of proinflammatory macrophages and granulocytes. This results in the CS termed as a macrophage activation syndrome (MAS) or secondary hemophagocytic lympho-histiocytosis (sHLH), thus leading to further tissue damage [79-81].

COVID-19 possesses different levels of various cytokines and chemokines through the mild to severe stage of the disease. The retrospective analysis has demonstrated that initial plasma levels of IL-1β, IL-1RA, IL-7, IL-8, IL-10, IFN-ɣ, monocyte chemoattractant peptide (MCP)-1, macrophage inflammatory protein (MIP)-1A, MIP-1B, granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor-alpha (TNF-α) are increased in patients with COVID-19. Furthermore, most patients with severe infection exhibit elevated serum levels of pro-inflammatory cytokines than

those in no severe infection, including IL-6 and IL-1β, as well as IL-2, IL-8, IL-17, G- CSF, GM- CSF, IP10, MCP1, MIP1α (also known as CCL3) and TNF, 1–4. Also, C- reactive protein and D- dimer are found to be abnormally high [82-85].

Increased D-dimer and fibrin degradation products levels, and prolonged prothrombin time have been associated with poor prognosis in patients infected by this 2019-nCov and who are at risk of developing disseminated intravascular coagulation (DIC). This could be explained by the excessive activation of the coagulation cascade and platelets and the imbalance between procoagulant and anticoagulant homeostatic mechanisms [86]. Thus, an important increment in the number of neutrophils, leukocytes, and the neutrophil-lymphocyte ratio (NLR) has been observed in severe COVID-19 compared to no severe cases. In addition, another important evidence is that the severity of COVID-19 is related to the level of the pro-inflammatory cytokines and subsets of immune cells [87, 88]. Lymphopenia indicates an impairment of the immune system and develops in most COVID-19 patients, especially in severe ones [89, 90]. Thus, it is one of the most prominent markers of COVID-19, It's also one of the diagnostic criteria for COVID-19 in China [91]. “Cytokine storm” and lymphopenia may have a major role in the pathogenesis of COVID-19 [92-94]. Therefore, it seems that neutrophils and leukocytes might reinforce the CS other than lymphocytes in COVID-19.

Moreover, in patients with COVID-19, the level of helper T cells (CD3+, CD4+) and cytotoxic suppressor T cells (CD3+, CD8+), and regulatory T cells are below normal level while helper T cells and regulatory T cells in severe patients are remarkably lower than non-severe patients. Regulatory T cells are responsible for the maintenance of the immune homeostasis with suppressing the activation, proliferation and proinflammatory function of most lymphocytes, including CD+4 T cells, CD+8 T cells, NK cells, and B cells [95, 96].

In the end, there are two possible reasons for the destruction of the immune system in patients with COVID-19, lymphocytes directly invaded by virus or indirectly damaged by CS. As we know that 2019-nCoV infects target cells through ACE2, while there was no ACE2 expression on lymphocytes, we speculate that lymphocytes were probably destroyed by CS.

Cancer and Covid-19 Pandemic:

1. ACE2 Expression in Various types of Cancer and Myelosuppressive Treatments: The fact that the cell receptor for SARS-CoV-2 is ACE2 [97]. It has raised questions about the relationship between the rennin-angiotensin system (RAS) and the severity of COVID-19. In addition, the expression of ACE2 was aberrantly expressed in many tumors cell growth and metastasis of pancreatic cancer, breast cancer, and colon cancer [98, 99]. It has been suggested that cancer increases the risk of COVID-19 because of ACE2 expression.

In view of the above, most patients with cancer are at a higher risk in general because of the ACE2 expression and myelosuppressive effects of treatment and their disease, which suppresses their immune system. In addition, SARS-CoV-2 infection in itself also causes lymphopenia, which further weakens the immune system.

Myelosuppression or bone marrow suppression is defined as a decrease in the ability of the bone marrow to produce blood cells. This may result in decreased red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia). Myelosuppression may occur when the stem cells in the bone marrow are damaged either by chemotherapy, by crowding of tumor cells or fibrosis, or due to bone marrow failure [100]. Therefore, in the setting of myelosuppression, there will be immunosuppression since the production of white blood cells is decreased. However, immuno-suppression does not always mean myelo-suppression. For example, a medication may suppress white blood cells or other parts of the immune system but not affect the red blood cells or platelets [101].

2. Renin-angiotensin System and ACE2 Receptor Expression in Patients with Cancer during COVID-19: Angiotensin-converting enzyme (ACE) mainly generates Angiotensin II (Ang II) by cleaving Angiotensin (1–9). AngII is a multifunctional bioactive peptide, induces vasoconstriction and has pro-fibrosis and pro-inflammatory properties, also stimulating the secretion of aldosterone by binding to the AngII type 1 receptor (AT1R) [102]. While ACE2 primarily

cleaves Ang II to produce angiotensin- (1-7). Ang-(1–7), is an active peptide with properties opposite to angiotensin II, which mediates biological activities such as anti-fibrosis, vasodilation, and anti-inflammatory through Mas receptor [103, 104].

The binding of SARS-CoV2 Spike protein to ACE2 attenuates ACE2 activity *via* internalization, creates an ACE/ACE2 imbalance with predominated of AngII with high levels, which leads to pulmonary vasoconstriction and inflammatory, oxidative, and fibrotic organ damage [105, 106]. Importantly, SARS-CoV2 by affecting ACE2/Ang-(1–7)/Mas receptor (MasR) axis may be harmful in patients with cancer during COVID-19 pandemic.

Numerous studies demonstrated the importance of RAS in patients with cancer. Although, Ang II via activation of AT1 receptors stimulate cell growth and plays an important role in the metastasis of different cancers by modulating proliferation, adhesion, migration invasion, and angiogenesis [107, 108].

In addition, Ang II enhances cancer stem cell -like phenotype in lung cancer cells by increasing the growth of cancer cells in a 3D culture and up-regulating CD133 levels [109]. And as demonstrated in cultures of human tumor cells from various types of cancer, blockade of the renin-angiotensin system, whether with an ACE inhibitor or an angiotensin II antagonist, reduces cellular proliferation and promotes apoptosis [110, 111].

The axis formed by ACE2 acts as a negative regulator of ACE activity and assumes a protective role against cancer [112]. Researchers have suggested that low ACE2 activity levels are frequently associated with the presence of cancer [113]. Further, an *in-vivo* study on xenografts of human lung cancer finds that ACE2 simultaneously suppresses expression of ACE and the AT1R and inhibits cell growth and the production of vascular endothelial growth factor-alpha (VEGFa). Moreover, the results in vivo prove that the overexpression of ACE2 reduces the invasive capacity and the migration of non-small cell lung cancer [114].

A study on the U-2 OS and MNNG-HOS osteosarcoma cells has shown that Mas mRNA and protein expression induced by the proinflammatory cytokine IL-1β, which was associated with a reduction of proliferation and migration. By contrast, Ender *et al.*, suggested that increased cell proliferation in osteosarcoma is led by small interfering RNA-mediated knockdown of Mas expression [115]. However, a previous study suggested that ACE2 might inhibit breast cancer angiogenesis and metastasis both *in-vitro* and *in-vivo* through suppressing the VEGFa/VEGFR2/ ERK pathway [116].

Vaccines and Treatments:

1. Potential Therapeutics: Many nations are diverting their best efforts for the implementation of appropriate preventive and control strategies; there are no specific antiviral drugs or vaccines for the control of SARS-CoV-2. Symptomatic treatment strategies are recommended for clinical practice [117]. In this review, we briefly discuss some of the investigational strategies and compounds that showed promising results based on their compassionate use and are currently in clinical trials as potential antivirals against COVID-19.

2. Antiviral Compounds:

2.1. Lopinavir-Ritonavir: Lopinavir-ritonavir is a combination of fixed doses of protease inhibitors used for the treatment of HIV [118]. It has been reported that the use of this combination has a good therapeutic effect in SARS and has been recommended for clinical treatment for COVID-19 [119].

2.2. Remdesivir: Remdesivir (RDV) is a mono-phosphoramidate prodrug of an adenosine analogue [120]. It is an investigational broad-spectrum antiviral drug with in vitro activity against multiple RNA viruses, including Ebola and CoV121. RDV was shown to have antiviral activity against SARS-CoV-2 *in-vitro* [122].

2.3. Ribavirin: Ribavirin was found to suppress the replication of human immunodeficiency virus (HIV) in peripheral blood lymphocytes, and was also reported to enhance the efficacy of zidovudine against HIV *in-vitro*. During the outbreak of SARS, ribavirin was broadly used for patients with or without concomitant use of steroids [123]. Ribavirin and IFN-β could synergistically inhibit SARS-associated CoV replication *in-vitro* [124].

2.4. Nelfinavir: Nelfinavir (NFV) is an anti-retroviral drug used in the treatment of the HIV.

NFV belongs to the class of drugs known as protease inhibitors (PIs), which has been shown to have a strong inhibition of SARS-CoV [125]. The antiviral activity of NFV against SARS-CoV-2 has been confirmed *in-vitro* and recommended for clinical treatment [126].

2.5. Chloroquine-hydroxychloroquine sulphate: Chloroquine is widely known for more than 70 years, is easily available, and affordable anti-malarial agent with proven chemoprophylaxis properties in malaria. Various mechanisms have shown it to have a role in SARS CoV infection, too. The SARS-CoV2 is known to bind to human cells *via* the ACE 2 receptor.

In-vitro studies have shown that the glycosylation process of ACE2 receptor gets affected thus causing the Vero cells pre-treated with chloroquine to be refractory to SARS-CoV infection that may be the mechanism through which even human cells can become refractory to this infection [127]. It has also been seen that treatment with chloroquine prevents the spread of SARS-CoV infection in the post-infection period [128].

3. Others:

3.1. Convalescent Plasma: Convalescent plasma is a safe and potentially effective strategy for the treatment of emerging and re-emerging pathogens, especially in those scenarios without proved antiviral agents or vaccines. Recently, CP has been widely recommended to be used for COVID-19 [129]. According to the physiopathology of COVID-19 severe patients should be privileged overcritical ones in order to reduce mortality and mortality.

3.2. Protective Monoclonal Antibody (Passive Immunization): Direct administration of monoclonal antibodies (mAbs) may play an effective role in CoV control as an intervention in exposed individuals.

It has been reported thatthemAbcan efficiently neutralize SARS-CoV and inhibit syncytia formation between cells expressing the S protein and those expressing the SARS-CoV receptor ACE2 [130]. However, mAbs can only recognize a single epitope, and the anti-infective effect may be limited. In addition, the development of mAbs requires a certain period of time, which is difficult to achieve in clinical application in a short time.

3.3. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPER) Antiviral Strategy: CRISPR-Cas adaptive immune systems defend microbes against foreign nucleic acids via RNA-guide endonucleases. Two class CRISPR-Cas systems (subtype VI-B) that lack Cas1 and Cas2 were identified and encompass a single large effector protein, Cas13b, along with one of two previously uncharacterized associated proteins, Csx27 and Csx28.

Through a combination of biochemical and genetic experiments, Cas13b appears to process its own CRISPR array with short and long direct repeats, cleaves target RNA, and exhibits collateral RNase activity [131]. It can be harnessed to target a wide range of single-stranded RNA (ssRNA) viral species that can potentially infect humans [132]. CRISPR RNAs (crRNAs) targeting conserved viral regions and identified functional crRNAs targeting SARS-CoV-2 were designed and screened. The CRISPR-Cas13-based strategy of PAC-MAN (prophylactic antiviral CRISPR in human cells), for viral inhibition, has shown experimentally that it could effectively degrade RNA from SARS-CoV-2 sequences and live influenza A virus (IAV) in human lung epithelial cells [133].

The CRISPR effector Cas13 could be an effective antiviral for ssRNA viruses because it programmable cleaves RNAs complementary to its crRNA [134].

4. Vaccine Development: Due to the rapid increase of SAR-CoV-2 infections and affected countries, vaccination probably offers the best option for COVID-19 control. By gaining knowledge from SARS and MERS vaccine development path, several research groups have been able to start SAR-CoV-2 vaccine development within only a few weeks after the outbreak.

Epitopes, mRNA, and Full-length spike (S) or S1, which contains RDB, might be considered as a good vaccine antigen because it could induce neutralizing antibodies that prevent host cell attachment and infection [135, 136]. Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform has been reported, and this technical advance is helpful for vaccine development [137] **Fig. 3**.

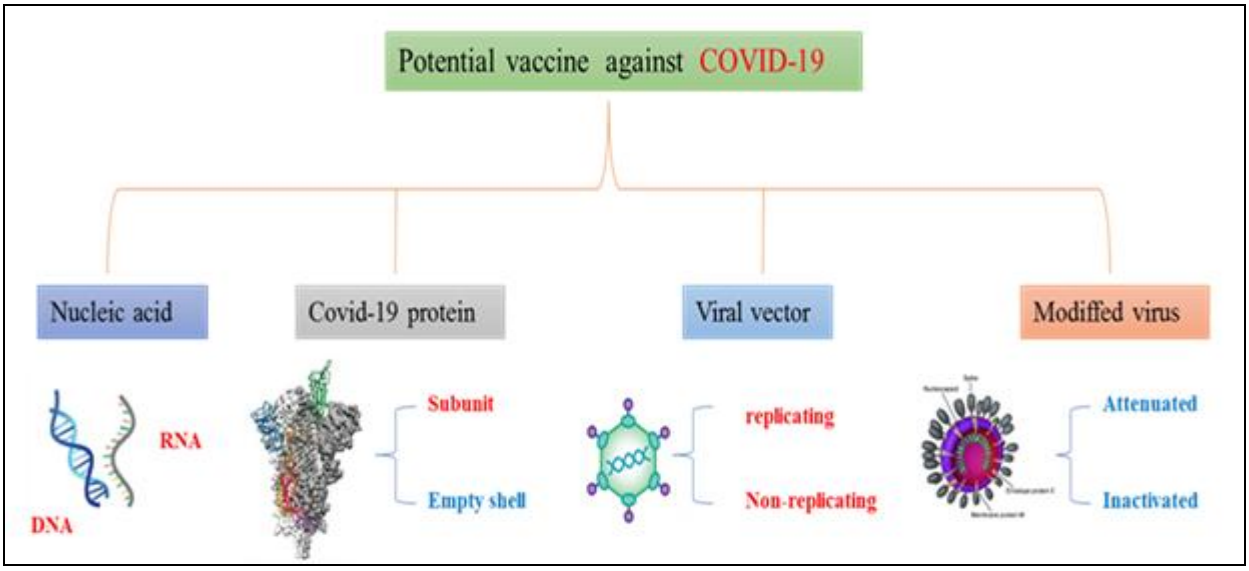

FIG. 3: STRATEGIES TO COUNTER SAR-CoV-2 CORONAVIRUS VACCINATION

CONCLUSION: In summary, SARS-CoV-2 is an emerging human CoV, and appears similar to previous SARS and MERS outbreaks. The most common factors behind COVID-19 mortality are older age and concomitant disease. The limited understanding of the pathogenesis of SARS-CoV-2 infection indicates that COVID-19 and SARS have similar pathogenesis and also have differences such as massive mucus secretion in both lungs of critical patient. There are still no specific antiviral treatments or vaccines available. However, the COVID-19 pandemic has the potential to overwhelm current health-system capacity. Postponing cancer treatments might be associated with some risk, although these risks will need to be considered in light of the magnitude of potential benefits, the impact of waiting times on outcomes, and competing for patient-level and system-level priorities. It is recommended that cancer patients receiving antitumor treatments should have vigorous screening for COVID-19 infection and should avoid treatments causing immuno-suppression or have their dosages decreased in case of COVID-19 co-infection.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: We declare no conflict of interest of any kind with anybody.

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How to cite this article:
Marref SE, Melakhessou MA, Marref C, Khattabi L and Becheker I: Immunosuppressive anti-cancer drugs may increase Covid-19 infection risks. Int J Pharm Sci & Res 2021; 12(2): 714-26. doi: 10.13040/IJPSR.0975-8232.12(2).714-26.