Review Paper
COVID-19 Vaccination and Cancer: The Most Critical Issues

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ABSTRACT

The lives of people all over the world have been affected by the coronavirus disease 2019 (COVID-19) pandemic since 2019. The virus originated in Wuhan City, China, and many people around the world are still infected with it daily, and many of them die. Following the prevalence of the virus, many countries were quarantined and came under economic, social, and medication pressure. As a result, various countries, including the United States, United Kingdom, China, and Iran, have begun to develop vaccines against SARS-COV-2 and have achieved great success. The Pfizer-BioNTech Comirnaty vaccine was the first vaccine against the virus that obtained World Health Organization (WHO) emergency use listing (EUL) on the last day of 2020 and promised hope for the people of the world. Clinical trials of the vaccines were not performed on all people including those with compromised immune systems such as cancer patients, or children under 12. Therefore, important questions arose: Are these vaccines available to everyone? Or do these vaccines protect everyone? As a result, studies were performed to evaluate the safety and efficacy of the vaccines in specific groups of individuals such as cancer patients. This review article addresses some of the ambiguities surrounding the vaccination of cancer patients and suggestions for improving their condition.

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1. Introduction

In December 2019, a new virus caused pneumonia in Wuhan City, China, which the World Health Organization (WHO) chose SARS-COV-2 (severe acute respiratory syndrome coronavirus 2) for a kind of single-stranded RNA virus and the disease called COVID-19 (coronavirus disease 2019) [1]. Because of its impact on so many people worldwide, WHO declared a pandemic for the condition caused by the virus in March 2020. This virus has spike (S), nucleocapsid (N), membrane (M), and envelope (E) proteins, which S glycoprotein are used for developing the current vaccines. The clinical spectrum of SARS-COV-2 infection ranges from asymptomatic infection through mild respiratory symptoms to severe disease, presenting with dyspnea and hypoxia, and a potential deterioration to respiratory failure, shock, multi-organ dysfunction, and fatal illness [2]. Almost 80% of cases get infected with mild disease including asymptomatic patients or mild pneumonia [3]. The main concern is for the elderly and people with medical comorbidities such as cancer because most patients need ICU care. In a study of 72314 patients with SARS-CoV-2 infection in China, the most common comorbid condition was cardiovascular disease accounting for 10.5%. Other common diseases were diabetes, chronic respiratory disease, hypertension, and cancer, with prevalence rates of 7.3, 6.3, 6, and 5.6%, respectively [2].

Pathogenesis of SARS-CoV-2

S protein is the most important one for the pathogenesis of SARS-CoV-2. Receptor-binding domain (RBD) of the virus's S protein attaches to the angiotensin-converting enzyme 2 (ACE2) receptors of human respiratory epithelial cells, and as a result, membrane fusion will occur [4]. The virus uses the host cells for the replication cycle and synthesis of its particles. Virus-induced double-membrane vesicles do not have any pathogen-associated molecular patterns, so the host immune system's pattern recognition receptors are not able to recognize them [5].Non-structural proteins play different and important roles in this pathogenesis; they hinder interferon (IFN)-I responses by various mechanisms such as suppression of the phosphorylation of signal transducer and activator of transcription (STAT) 1. They are also antagonists of cytokine production as they disrupt the nuclear factor-kappa B (NF-KB) signaling pathway. Furthermore, they provide the host's mimic 5' cap for the virus; as a result, host immune cells can not recognize the viral RNA genome [6].

The D614 G mutation that occurs in the S protein, modifies the phenotype of SARS-CoV-2, according to the clinical and in vitro evidence. Although the effect of this mutation on other aspects such as vaccine effectiveness and pathogenesis has not been cleared yet [7].

Diagnosis of COVID-19

Diagnosis of COVID-19 has various procedures. Clinical features are the first part of the diagnosis process. The symptoms include fever, fatigue, dry cough, dyspnea, myalgia, and breathlessness. Gastrointestinal symptoms such as diarrhea and anorexia were seen in some patients; some do not have any respiratory symptoms or fever [8].

Although there is not any specific blood test for the diagnosis of COVID-19, nonspecific ones can be helpful. The complete blood count of these patients usually is normal or shows lymphopenia and a decrease in white blood cells. The results of inflammation measurement tests such as C-reactive protein and erythrocyte sedimentation rate are not normal and demonstrate an increase in them [9]. CPK, LDH, D-dimer, creatinine, prothrombin time, and ALT/AST are other factors that rise in these patients [10].

Imaging is another helpful way the diagnosis this disease. Chest X-ray demonstrates patients' patterns, and the severity and duration of illness can be diagnosed by this method. Nevertheless, to measure the progression of the disease and the effect of treatment, computed tomography (CT) imaging is necessary. The notable point is that the detection rate of chest CT (98%) is higher than reverse transcriptase polymerase chain reaction (RT-PCR) (71%) [11].

The most common detection and the gold standard test is quantitative RT-PCR. In this test, the S antigen of SARS-CoV-2 is searched. The reverse transcription loop-mediated isothermal amplification (RT-LAMP) is another molecular test that indicates the amplified DNA with pH-sensitive or fluorescent dye. This test is simpler, faster, cheaper, and at least equal to RT-PCR in terms of specificity and sensitivity [12].

Other diagnostic techniques are not widely used including immunological techniques such as immunofluorescence assay, N protein detection assay, and direct fluorescence antibody test, and some novel techniques such as next-generation sequencing (NGS)-based technique, droplet digital PCR (ddPCR), and Penn RAMP technology [10].

Different types of COVID-19 vaccines

The types of vaccines available for COVID-19 are as follows:

Live weakened virus vaccines are the oldest type that measles, mumps, rubella (MMR) vaccine is the famous attenuated virus combination. COVI-VAC (Codagenix) is an attenuated COVID-19 vaccines. Although this type of vaccine has a very high stimulation and as a result, it produces a stable and strong response, it is not suitable for people with weak immune systems such as cancer patients under treatment and children.

In the inactivated type of vaccine, the killed or fully destroyed virus through heat or chemicals is used. Hepatitis A, Influenza, Typhoid, and Polio are existing examples of this type. Sinovac-CoronaVac, Sinopharm, COVIran Barakat, and Bharat Biotech BBV152 COVAXIN are inactivated COVID-19 vaccines. This type of vaccine produces relatively weak cellular immunity, requires booster doses, and is expensive.

Hepatitis C and human papillomavirus (HPV) vaccines are produced based on using one or more types of antigens including proteins, peptides, or polysaccharides. Novavax and AdaptVac are sorts of subunit COVID-19 vaccines. Vaccines based on subunits have a lot of positive aspects such as usability for almost everyone, even people with compromised immune systems, and rare side effects. Stimulation of the immune system by these vaccines is more effective than inactivated vaccines and weaker than live vaccines. Demerits are the requirement of the adjuvant and hard production process.

University of Oxford and Astra-Zeneca, CanSino Biologics, Johnson and Johnson, and Sputnik V are viral vector vaccines. To produce these vaccines, a viral vector transmits its genetic part to the human body. The pros of viral vectors are high safety, high specificity and as a result a strong response, and stimulation of both humoral and cellular immunity. The cons are all about the viral vector used for the vaccine and the possibility of developing an immune response against them as well as causing diseases.

DNA and RNA vaccines are the latest and newest types of vaccines, which were not available before the COVID-19 pandemic. Moderna and Pfizer are based on RNA and Inovio is based on DNA. The merits of these vaccines are that they are affordable and easy to design, affect both humoral and cellular immunity, and the immune response generated against the antigen is highly specific. The problems are such as the need for cold transmission chains and the probability of inducing immunologic tolerance [13].

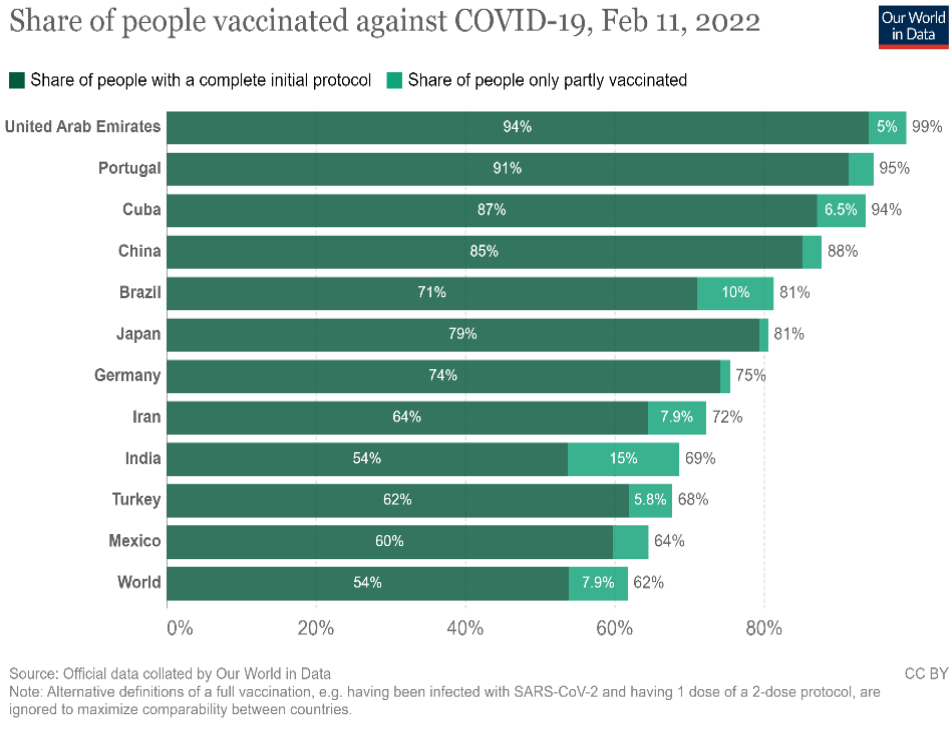

Figure 1. Several people vaccinated against COVID-19 in some countries injected the first and second doses by February 12, 2022 [18]

Importance of vaccination

According to the WHO, as of 11 February 2022, almost 405 million people worldwide were infected with the virus, and about 5 million people died from the disease [14]. In Iran, from 3 January 2020 to 11 February 2022, there have been more than 6.7 million confirmed cases of COVID-19 reported to the WHO among which 133294 died [15]. In addition, the global impact on sectors such as public health and the economy was catastrophic due to general constraints and quarantine [16].

Vaccinating all people is the only sure way to save people against this pandemic [17]. By 12 February 2022, more than 10 billion vaccine doses were administered worldwide, and 1346 million doses in Iran. Vaccine injection statistics in the world, Iran, and some leading countries in this field can be seen in Figure 1 [18].

According to studies, 75% of the world's population should be vaccinated, and vaccines should be at least 80% effective to stop this pandemic. Although vaccination has not been entirely performed, the incidence and mortality rate has been reduced. Even if the vaccine does not control the epidemic, it is still the only safe and valuable way because it can prevent the death of many people, reduce the severity of the disease, and hospitalization, to reduce costs [19].

Efficacy of vaccines against new variants

Since there is a mutation and new variants like all viruses, it is normal to have different variants of SARS-CoV-2. Alteration and deletion of amino acids of S antigen cause new variants and reduce the effect of antibodies against this virus. So far, ten variants of the virus have been observed including alpha, beta, gamma, delta, epsilon, eta, kappa, lambda, mu, and the last variant, SARS-CoV-2 Omicron variant (BA.1/B.1.1.529), which was reported to the WHO in November 2021 [20]. The presence of these variants, especially Omicron, which could escape the vaccine-induced antibodies using the RBD, raised concerns about the effectiveness of vaccines to end the pandemic [21]. Therefore, increasing information on the efficacy of available vaccines on different variants is essential.

In a systematic review, 35 research articles have been reviewed related to alpha (B.1.1.7), beta (B.1.351), gamma (P.1), and delta (B.1.617.2) variants with different types of studies such as phase 1–3 clinical trial results. It was concluded that the available vaccines have an acceptable level of protection against the studied variants, especially in people who received two doses, and are most effective against the alpha variant. As aging affects naïve and $CD8^+$ T cells and there is also a decrease in the function of $CD4^+$ T cells, the vaccine's effectiveness is unclear to these people. However, according to the results of research conducted specifically on the elderly population, it can be concluded that vaccines provide a logical response to different variants in these people and prevent severe disease and death [16].

In a study by Edara et al. the vaccine's efficacy in different individuals who received the BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccines against the Omicron variant was studied. The study groups included people who received two doses of the vaccine (2-4 weeks and six months after receiving the vaccine), those who received the booster (third) dose (1-4 weeks after receiving it), and people who had a history of COVID-19 infection and have been receiving two doses of the vaccine six months ago. Only 21% of people who received two doses of the vaccine and 55% of vaccinated people with a history of COVID-19 showed good protection against this variant. In comparison, more than 90% of people who received the booster dose showed remarkable activity against the Omicron variant. From these results, it can be concluded that only the third dose can prevent the recurrence of this virus in the world [22]. In another study, the sera of people receiving these two vaccines against wild type and delta and Omicron variants were studied. The results of this study also indicated the importance of receiving a booster dose to combat the virus [23].

In another study, Naranbhai et al. evaluated the effect of available vaccines in cancer patients against alpha, beta, gamma, and delta variants. According to the results, it was concluded that current vaccines have a response against different variants, especially against beta in comparison with wild type. Also, they opine that the booster dose in cancer patients, even in non-cancer individuals with inadequate neutralization antibodies, can make an acceptable and safe response for them [24].

Cancer patients

Given the importance of vaccination for most people globally, it must be decided whether or not to vaccinate high-risk groups. The most critical or fatal disease occurs predominantly in hospitalized adults with advanced age or specific underlying medical comorbidities, including cancer [25, 26] because their immune system is not normal, as the tumor or their treatment caused compromised immune status. Adult oncological patients infected with COVID-19 often have severe diseases [27, 28]. Because

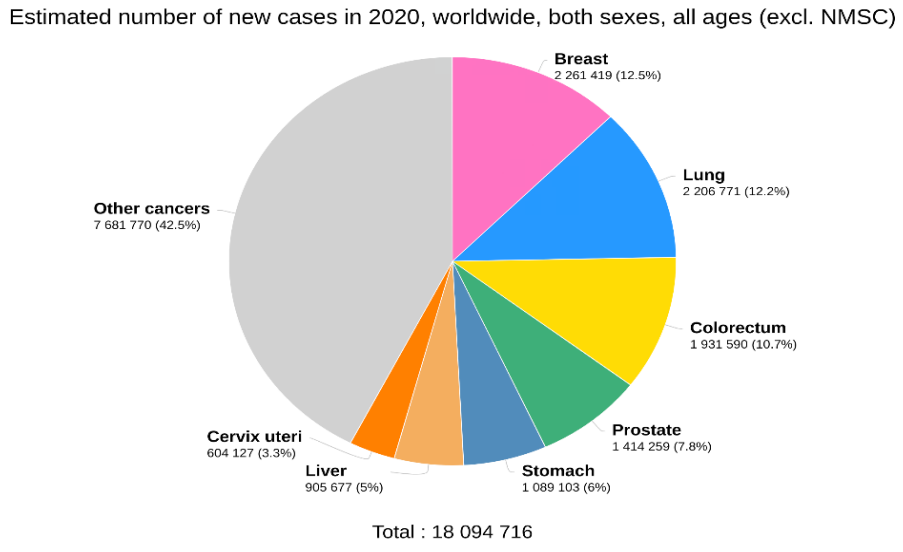

Figure 2. Estimated number of new cancer cases all over the world for both genders and all ages reported by IARC [29].

of their condition, these patients should prioritize COVID-19 vaccination. According to the WHO's international agency for research on cancer (IARC) statistics, 18 million new cancer cases were reported in 2020 among which the most common cancers were breast and lung. The full information can be seen in Figure 2 [29].

In addition to the devastating effects of this epidemic on the living conditions of the people, the mental state, human relations, economic conditions, and other conditions of all people of the world, this situation was much worse for people with cancer. Not only are these people at greater risk of developing a severe illness, but their treatment is delayed, exacerbating the disease, and resulting in their death. According to studies, the mortality rate due to infection with COVID-19 in people with cancer is higher than in people without cancer [30]. In a study of 3801 patients with hematological malignancies (HM), including lymphoproliferative and myeloproliferative malignancies, 73.1% of the patients were hospitalized, and 31.2% died. Patients with myelodysplastic syndromes had the highest rate of mortality (118279, 42.3%). This study suggested that COVID-19 vaccinations would significantly reduce infection in HM patients, although the likelihood of vaccination being less effective should be considered [31].

In a study by Naranbhai et al. performed on 750 cancer patients, it was observed that the humoral immune response in these patients was weaker than in the non-cancer control group. Also, they found that in both groups, mRNA vaccines including mRNA-1273 and BNT162b2 vaccines are substantially more immunogenic than Janssen Ad26.COV2.S vaccine. Besides, people with a history of infection with COVID-19 had a more robust response. Moreover, they believe that a booster dose is the only way to compensate for poor responses [32].

Since vaccination is the only necessary way to increase the immunity of cancer patients against this virus, they should be vaccinated, if possible, according to each individual's condition and their doctor's opinion. Otherwise, we will have to witness the death of many of these people and, as a result, the psychological, economic, social, and medical pressures on society.

The individual condition of each cancer patient depends on the type and stage of cancer and the type of treatment each person receives. In the following, the possibility of the effectiveness of this vaccine on cancer patients with different therapies will be investigated.

The effect of treatments received by cancer patients on vaccine immunogenicity

The immunogenicity of the vaccine varies depending on the effect that the treatment has on the individual's immune system. Suppose treatment weakens a person's immune system. In that case, there are two different possibilities. Firstly, due to the weakening of the immune system, the vaccine's effectiveness will decrease, and these people will not have good immunity against the vi-

rus. In the second case, due to the weak immune system, these patients may have a high response to the vaccine or the vaccine may cause other diseases in these people. Therefore, the effectiveness of each treatment should be considered separately.

Immune checkpoint inhibitors (ICI)

ICI are a good treatment for patients with lung, kidney, neck, head, and melanoma cancers. So, a significant number of cancer patients benefit from this treatment [30]. Unlike other treatments, this treatment strengthens the immune system instead of weakening it by targeting immunosuppressive pathways such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The amount of these proteins in the T cells responsible for reacting to the tumor increases in cancer patients, so the immune system can fight cancer by blocking these proteins.

While lung cancer and smoking exacerbate COVID-19 infections, more than half of these patients need to be hospitalized after the disease, and a quarter of them die. ICI treatment has not been associated with more severe infections or mortality in patients with lung cancer [33].

In a study, Naranbhai et al. found that those receiving immune checkpoint blockade had higher antibody titers [32].

Lasagna et al. performed a study on 60 cancer patients receiving immunotherapy three weeks and six months after SARS-CoV-2 vaccination. IgG concentration reduced by 88% in patients without a history of SARS-CoV-2 exposure and by 2.1% in patients whit a history of infection [34].

In these patients, because the drug boosts the immune system, the vaccine may trigger a robust immune response, causing severe inflammation and, as a result, damage to organs. Consequently, they have to receive corticosteroids or other immunosuppressant drugs, so these drugs affect anti-spike IgG titers. As a result, they do not have the necessary immunity against this disease. Some studies have been performed on these patients and found that they did not have immune-related adverse events (irAEs) after receiving the vaccine [35, 36]. Therefore, more studies are needed to decide whether to vaccinate patients receiving ICI immunotherapy, and monitor these patients during the process.

Cytotoxic chemotherapies treatment

In patients undergoing cytotoxic chemotherapy, the immune system is not entirely suppressed, and the body of these patients can produce an immune response. In a study of 229 cancer patients receiving chemotherapy, 223 responded to the mRNA-1273 COVID-19 vaccine and had sufficient antibodies [37].

Because cytotoxic chemotherapy interferes with DNA replication, cell cycle synthesis, and progression and suppresses lymphocytes through these treatments, vaccination is not expected to be significantly effective in these individuals. However, the suppression is not complete, and nevertheless, immune responses to vaccination can be induced during cytotoxic chemotherapy. According to the results of Naranbhai et al. the antibody level of cancer patients who received or are receiving chemotherapy is lower than patients with different therapies such as immune checkpoint blockade, and they suggested the booster dose for these patients [32]. In general, due to the favorable results obtained from the vaccination of these individuals against influenza, pneumonia, and Hepatitis B, except for intensive chemotherapy courses, patients undergoing chemotherapy are expected to develop protective responses with COVID-19 vaccination.

Radiation

A study of 9365 hospitalized patients in Germany found that during the COVID-19 lockdown, radiotherapy for head and neck cancer patients became more common. In contrast, usage of this treatment for cervical cancer patients decreased [38]. So, this is so important to investigate the efficacy and side effects of COVID-19 vaccines in patients with malignancies treated with radiotherapy.

Although radiation therapy to a large part of the body affects marrow, the effect of this treatment on the immune system is infrequent (in situations such as before stem cell transplantation in which the whole body is irradiated, or total lymph node irradiation). In these cases, it is recommended not to vaccinate these patients, vaccinate those around the patient, and take the necessary steps to prevent them from contracting COVID-19 with greater sensitivity. Also, if possible, the person's treatment should be changed to benefit from the protection provided by the vaccine [39].

Targeted therapies

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein activated by binding a specific

epidermal growth factor (EGF) ligand. This activation causes uncontrolled proliferation due to tyrosine phosphorylation by kinase domains. Studies have shown that the EGFR family has a crucial role in developing and progressing many cancers, such as colorectal cancers, breast cancers, and ovarian tumors [40, 41]. There are three generations of tyrosine kinase inhibitors that are used as targeted therapies. These inhibitors compete with Adenosine 5′ triphosphate for binding to the intracellular domain of the EGFR tyrosine kinase, so EGFR autophosphorylation and, as a result, downstream signaling are inhibited [42]. Another advanced anti-EGFR therapy is anti-EGFR monoclonal antibodies, which bind to the extracellular domain of EGFR and create competition for ligands binding [43].

Due to the mechanism of targeted therapies, direct immunosuppression by this treatment is not expected, but it may affect the process of antibody production. Previous studies on the effectiveness of the influenza vaccine in cancer patients undergoing this treatment have shown acceptable immunity in these patients [44, 45]. Therefore, the COVID-19 vaccination is expected to provide reasonable protection for cancer patients undergoing targeted therapies.

Lymphodepleting or B Cell depleting therapies

Using monoclonal antibodies, including anti-CD20 and anti-CD38, is a kind of treatment that depletes B cells and lymphocytes in hematologic malignancies, autoimmune diseases, and multiple myeloma. Anti-CD20 treatments induce peripheral B cell aplasia for at least four months, and these cells are the main features for producing antibodies. As a result, T cell reduction will occur because of a decrease in B cells' antigen-presenting. Therefore, during this period, immune responses to vaccination are impeded [46].

Addeo et al. enrolled a total of 140 patients with cancer who received the BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine. One hundred thirty-one patients were identified as SARS-CoV-2 naïve by anti-SARS-CoV-2 N protein IgG test and 81% of these patients after the first dose and 94% of them after the second dose achieved antibody protection. Patients who received the anti-CD-20 antibody six months before did not achieve antibody protection. Antibody titers produced in solid tumor subjects were higher than in patients with hematological malignancy [47].

A study of 116 haemato-oncological and rheumatological disease patients who received two doses of a SARS-CoV-2 vaccine with a history of treatment with anti-CD20 B cell-depleting agents showed that vaccine responsiveness in these patients is weaker than healthy controls [48].

Anti-CD38 therapies are one of the possible treatments for patients with multiple myeloma. Plasma cells are the target of these antibodies, and consequently, $CD19^{+}$ B lymphocytes will be depleted as well. However, some plasma cells are expressing reduced levels of CD38, and therefore, they can hide from monoclonal antibodies. These cells may be able to produce the least amount of antibodies in response to vaccination to protect against this disease [49].

Ghandili et al. performed a study on 82 multiple myeloma patients with different types of treatments such as anti-CD38 directed therapy (45.1% of patients) and various types of vaccination, including mRNA-based, vector-based, and heterologous. Generally, 20-30% of patients after the first dose and 88% after prime-boost vaccination produced adequate antibody titer [50].

Chimeric antigen receptor T cell (CAR-T) therapy is a kind of adoptive cellular immunotherapy that uses patients' T cells to fight cancer cells. Each CAR is designed for an antigen; so, it is specific to cancer. In hematologic malignancies, these cells are made against CD19 and B cells are their target. Generally, the infection risk in recipients of this immunotherapy is high, and therefore, they are in danger of getting infected with SARS-CoV-2. Usually, they are not included in the study of the efficacy and safety of SARS-CoV-2 vaccines, and consequently, there is not much data about these people. Because this treatment reduces B cells, the response to the vaccine is not expected to be acceptable in these people. Some studies have been performed on a small number (n=12 and 14) of cancer patients undergoing CAR-T cell therapy that are consistent with this hypothesis [51-53]. Most of the committees such as the national comprehensive cancer network (NCCN), American society of transplantation and cellular therapy, American Society of hematology, and NCCN recommend that mRNA SARS-CoV-2 vaccines should be administered at least three months after CAR-T therapy [54-57].

Overall, patients with HM undergoing anti-B cell therapies have a suppressed immune system and are at high risk for other diseases such as COVID-19. So, vaccination of these individuals is necessary. Otherwise, the response is not as strong as healthy people.

Clinical trial for cancer patients

In a study of some cancer patients hospitalized and their family members, most of them underwent chemotherapy and were over 40 years old. In general, 65% of these patients refused to be vaccinated, while 67% of their family members agreed to be vaccinated. The reason most people accepted to be vaccinated was to protect their family members against infection. Other reasons were the safety and effectiveness of the vaccine. Other cancer patients and their families refused to be vaccinated because they did not trust the vaccine's efficacy and feared side effects [30]. Therefore, to reassure this group of people, clinical studies about the effectiveness of the vaccine and its side effects on cancer patients should be explicitly performed. Special considerations should be considered depending on the type of treatment these individuals receive and the study phase.

Possible solutions for cancer patients

Because the immune response caused by the vaccine is weaker in cancer patients than in healthy people, it is better to use ways to strengthen the immune system for these people.

Anti-PD-L1 treatment

ICI such as anti-PD-L1 treatment are a type of immunotherapies, which is very common for cancer patients these days. As already described, this treatment can positively affect the immune system and strengthen it, so these patients may have to take immunosuppressants to get the vaccine. Given that the immune system is weakened in cancer patients, this treatment can play a bilateral role for these patients.

One particular interest lies in the dual character of anti-tumor treatment for physicians and researchers. For instance, ICIs can activate both innate and adaptive immune systems and they can cause pneumonitis and thrombocytopenia as well [58, 59]. Besides, although lung disease and problems are among the most critical risk factors for COVID-19, lung damage is not a common complication of ICIs treatment.

In a cohort study of 423 cancer patients infected with COVID-19, the results showed that the risk of hospitalization and severe disease was higher in people over 65 and those who received ICIs [60]. On the other hand, in another study performed on lung cancer patients with COVID-19, no relationship was observed between disease severity and treatment [33].

Qin et al. performed 10X scRNA-seq on isolated PBMCs of 4 cases with and four patients without cancer after their remission of COVID-19 and three healthy donors. They found that there is a considerable increase in the number of cytotoxic T cells, NK cells, and NKT cells in patients undergoing anti-PDL1 treatment. Moreover, as SARS-CoV-2's clonal expansion of cytotoxic T cells is one of the other impacts of anti-PD-L1 therapy, it can protect these patients from reinfection [61].

As can be seen, the results of the studies are very different, and more studies are needed to detect the exact effect of this treatment.

Vaccine formulation strategies using nanomaterials

Nanoparticles can inactivate viruses, bacteria, fungi, or yeasts through photocatalysis-induced reactive oxygen species generation or photothermally and have intrinsic antipathogenic properties to be used as disinfectants in healthcare settings. They can also be used as treatments; for example, for the treatment of SARS-CoV-2, nanomaterials can be used as drug carriers to the lung [62].The use of nanotechnology for vaccine development has many merits; for instance, antigens are delivered to a specific site, intracellular uptake is improved, controlled release is performed, side effects are reduced, and immunosuppressive activities and prevention of premature degradation of antigens increase immunity. Nano-based formulations can be used as carriers or adjuvants in vaccine development [63]. The ability of these materials is extraordinary; nanoparticles can be used to design a vaccine that can both stimulate the immune system and counteract the cytokine storm by suppressing the immune system.

Sekimukai et al. claimed that gold nanoparticles that are functionalized with S protein induced an antigen-specific response [62]. Some nano-based vaccines for SARS-CoV, such as mRNA-1273 (developed by Modena) and NVX-CoV2373 (developed by Novavax company), are lipid-nanoparticle-encapsulated mRNA-based and glycoprotein nanoparticle vaccines, respectively. This kind of vaccine can be used for individuals with immune system problems, including cancer patients because, in addition to being safe, it is very effective in these patients [63].

Thymosin α1

In human childhood, the thymus produces thymosin α1; but in adulthood, this production stops. The amino acid sequence of chemically synthesized Tα1 is the same

in the thymus gland's isolated thymosin α1. It has lots of effects, such as the modulation of immune cells in different ways depending on the immunological status of the host [64]. One of the uses of thymosin α1 is its combination with ICI, which causes a synergistic effect and increases safety in this drug by preventing opportunistic infection [65]. For example, in a study, they used a combination of thymosin α1 and an anti-PD-1 antibody and found that this combination increased the effect of the anti-PD-1 antibody in the metastasis model [66]. In addition to cancer, this drug has been used alone to treat diseases such as Hepatitis B and severe sepsis, and good results have been obtained [67, 68].

Carraro et al. performed a pilot study about the immunogenicity of the pandemic H1N1v influenza vaccine alone and combined with thymosin α1 on hemodialyzed patients. The results showed an increasing effect of thymosin α1 on the immunogenicity and safety of this vaccine [69].

Thymosin α1 against COVID-19 can have different functions including increasing the imbalance of IL-4 and IFN-γ in $CD4^+$ T cells, helping to identify infected cells, and controlling T cell activity [70]. In children, thymosin α1 is produced by the thymus, and this may help children with COVID-19, and statistics from children with SARS-COV-2 confirm this possibility [71]. COVID-19 is also more severe in the elderly, whose thymus is the cause of a weakened adaptive immune system confirming this hypothesis [72]. Because thymosin α1 is well tolerated and has no drug interactions, it can also regulate immune homeostasis well, and because of its pleiotropic function, it makes various adjustments to the immune system. So, this drug is recommended to fight COVID-19.

Monoclonal antibodies

Nowadays, there are a lot of clinical trials performed to measure the effectiveness of monoclonal antibodies on COVID-19 treatment. Some of them include bamlanivimab-etesevimab and casirivimab-imdevimab combinations and the monotherapies with sotrovimab and regdanvimab approved by food and drug administration (FDA) for emergency use [73, 74]. Most of these neutralizing monoclonal antibodies are derived from recovered patients' plasma and are against the RBD of SARS-CoV-2's S protein [75]. This domain of the S protein interacts with the ACE2 receptor, and mAb breaks this interaction by binding to this protein [76].

It is necessary to find a certain way for high-risk groups, including treatment staff, unvaccinated people, and people with weakened immune systems such as cancer patients. The use of neutralizing mAb as a post-exposure prophylaxis agent is beneficial because of its potential. Various studies have been performed to evaluate the effectiveness of antibodies for prevention, and in all these studies, the results show the effectiveness of this drug to prevent COVID-19 disease [77, 78].

Taken together, given the purity of these antibodies and the fact that the only FDA-approved treatment is remdesivir, further studies on the therapeutic effects and prevention of these antibodies could lead to improved results.

FDG PET/CT and COVID-19 vaccination

[^{18}F]-2-fluoro-2-deoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a kind of imaging that is used to monitor the tumor closely and treatment response monitoring in cancer patients who are undergoing therapy. Usually, anatomic alterations occur after functional-metabolic changes, and FDG PET/CT is a reflection of these changes. So, this imaging is used to evaluate the response during and after treatment. Furthermore, FDG PET/CT helps identify features of the tumor, such as hypoxia and metabolism. Thus areas that have not responded to treatment will be identified, and the healing process improves [79].

Reactive ipsilateral axillary lymphadenopathy can be counted as a side effect of COVID-19 vaccine administration that has been reported by doctors and radiologists [80, 81]. FDG uptake on FDG PET/CT and lymphadenopathy can lead to misdiagnosis by clinicians. Lymph node swelling in COVID-19 infected patients is reported, and it is a result of rising monocytes in lymphoid tissue because of FDG uptake [82, 83].

Lymph node enlargement also occurs after COVID-19 vaccination, suggesting benign lesions; under the circumstances, it can also indicate malignancy. Skawran et al. performed a study on one hundred forty patients who received their first or second dose of Pfizer-BioNTech or Moderna and were referred for FDG PET/CT. In 54% of these patients, symptoms of FDG uptake by lymph nodes were observed on the same side of the vaccine injection [84]. The critical question is whether swollen lymph nodes can be selected as a biomarker to determine the effectiveness of the COVID-19 vaccine in individuals?

One of the problems for cancer patients in this area is misdiagnosis and subsequent unnecessary treatment if the doctor is not aware of the patient's vaccination and their FDG PET/CT false-positive result. Radiologists need accurate information about the time and site of a patient's vaccination, as well. To avoid these challenges, oncologists and radiologists should communicate with their patients and be aware of their vaccination schedules. Moreover, the best time to FDG PET/CT is 4-6 weeks after vaccination, although lymph node problems associated with vaccination are still seen in some patients 7-10 weeks after vaccination [85].

2. Conclusion

Vaccines have always been the savior of mankind and have eradicated many infectious diseases. The coronavirus epidemic has caused many problems in the lives of people around the world. Ten months after the pandemic, the first vaccine received the WHO emergency use listing procedure (EUL), and after 2 years, the incidence and mortality rate of this virus has been greatly reduced thanks to the vaccine. In some countries, including Iran, the daily mortality has reached zero. Giving this vaccine to cancer patients was a big risk because of their immune systems and the treatments they received. Moreover, many of them died because of the virus or because of delays in their treatment due to the pandemic. Clinical studies were performed on these individuals and different results were obtained based on various factors such as type of cancer, disease severity, type of treatment, and type of vaccine. Some groups responded well to the vaccine, and some received medications to boost the immune system. With due attention to the fact that everybody should receive adequate medical care facilities, we recommend that more clinical trials be performed for cancer patients undergoing active treatment so as a result of them, these patients can be safe against this type of disease by appropriate vaccination.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research

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Authors' contributions

The authors declared no conflict of interest.

Conflicts of interest

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