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COVID-19 and Anti-Cancer Therapies

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Abstract: ***The severe acute respiratory syndrome CORONAVIRUS 2 (SARS-CoV-2) has caused a global pandemic, and cancer patients, along with the people who have a history of cancer, are in the high-risk category, different anti-cancer therapies that help reduce and prevent tumors through immunosuppression can have adverse effects with the COVID-19. If the function of T and B cells is impaired, the patient will not be able to mount an adequate immunity even after vaccination. However, some anti-cancer regimens can work with the system and against viral infection. This review focuses on the positive and negative effects of different anti-cancer therapies and how they affect COVID-19 vaccine efficacy.***

Keywords: Anti-cancer therapies, cancer, COVID-19, pandemic, vaccination, immunity

1. Introduction

The COVID-19 pandemic is a wide spread infectious disease caused by the severe acute respiratory syndrome CORONAVIRUS 2 (SARS-CoV-2). It spreads from person to person via the transfer of liquid droplets when the infected patients cough, breathe, sneeze or talk. Symptoms can range from mild to severe depending on the person's health and other risk factors. These risk factors are old age, male sex, and underlying medical conditions like heart problems, diabetes, cancer, or respiratory illness. Common mild symptoms include cold, fever, fatigue, dry cough, loss of smell and taste, and headache. In case of severe disease, patients experience shortness of breath, chest pain, sudden confusion, or even stroke (Coronavirus, 2021) [1]. Cancer patients and people with a history of cancer are at risk of developing severe disease and high death rates. This can be due to the weakened immune system caused by tumor growth, anti-cancer therapies, or high interaction with hospital environments for treatment. Patients with lung cancer seem to be most affected, followed by those with hematological malignancies (Yang et al., 2020) [2]. Depending on their specific type, Haematological tumors can affect T cells or B cells, or both. Many studies show that disease severity and mortality rate are higher in hematological tumor patients than in solid tumor patients. This is because of impaired immune system mechanisms in the former (Desai et al., 2020) [3]. There are many studies about the effects of anti-cancer therapies on COVID-19 disease progression. This review discusses the negative and positive effects of some of these therapies and whether cancer care needs to take backstage while dealing with the pandemic.

Anti-Cancer Therapies and COVID-19 Disease Progression

There are contradicting papers regarding the effects of different anti-cancer therapies and COVID disease. Patients with severe COVID-19 were more likely to have undergone chemotherapy, radiotherapy, targeted therapy, surgery, or immunotherapy than those with non-severe disease. They also found that the risk of COVID-19 severity and death was highest for patients with the last chemotherapy treatment within two weeks of admission and decreased as the time interval since the last chemotherapy increased, with maximum safety when the last treatment was at least three weeks before disease start (Tian et al., 2020) [4]. Some others (Wang & Huang, 2020, Tian et al., 2020, Barlesi et al., 2020, Al-Quteimat & Amer, 2020, Ohara et al., 2021) [5, 6, 7, 8] also observed that recent chemotherapy (<28 days) increased the risk of death. Wang & Huang showed that the association between chemotherapy and severity of COVID-19 was significantly modified by time interval and intensity of cycles. Also, immunotherapy within three months of infection increased the risk of exacerbation (Wang & Huang, 2020) [4]. There is a risk of interaction between anti-cancer drugs and drugs given to control COVID-19 prognosis, especially in cancer patients due to their underlying disease, older age, and consumption of multiple medications. For example, there is a chance that consuming concurrent CQ or HCQ could affect the efficacy of tamoxifen, an anti-cancer drug, in breast cancer patients (Jafari, Dadkhahfar & Perseh, 2020) [9].

There are many studies (Wang & Huang, 2020, Huang et al., 2020, Wu et al., 2020, Luo et al., 2020, Lin, Chen & Han, 2021, Ma, Yin, Qian & Wu, 2020, Akula et al., 2020, Liu, Lu, Wang, Liu & Zhu, 2020) [4, 10, 11, 12, 13, 14, 15, 16]that observed no statistically significant correlation between anti-cancer therapy (including surgery, chemotherapy, targeted therapy, immunotherapy, and radiotherapy) and COVID-19 disease severity or mortality. One study (García-Suárez et al., 2020) [17] observed that active treatment with hypo ethylating agents was associated with 53% lower mortality.

Immune check point inhibitor (ICI) therapy has contradictory effects on COVID-19diseaseprogression, and the disease by itself has a certain influence on ICI therapy efficacy. ICI therapy is a type of immunotherapy for solid tumor patients. On the one hand, they aggravate the cytokine storm, and on the other, they contribute to the recovery of immune competence, which plays a protective effect against the viral infection. ICI treatment may activate the immune system by inhibiting the

immunologic impairment of T-cell number and function induced by COVID-19 infection. It may also reduce the severity of the disease through viral clearance. On the other hand, ICI therapy can favor COVID-19 disease from worsening in later stages by promoting different immune-activating mechanisms (Maio et al., 2020) [18]. It can disrupt self-tolerance and lead to immune-related adverse events in multiple organs, including ICI-induced pneumonitis. Furthermore, the PD-1/PD-L1 axis, through which ICI therapies exert their anti-tumor response, also regulates antiviral responses, and it's up regulation has been observed during viral infection (Lovly et al., 2020) [19]. Wu et al. observed a higher proportion of severe COVID-19 in cancer patients who received ≥ three cycles of ICI, but this was not statistically significant. Like the study by Luo et al., they did not observe an association between the interval of last ICI administration and COVID-19 severity (Luoet al., 2020, Wu et. al., 2020) [19, 11].

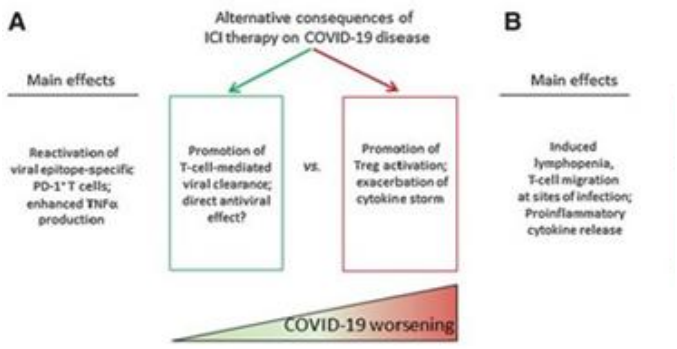

Figure 1: Effects of ICI therapy on COVID-19 disease and vice versa (Maio etal., 2020) [18]

Doctors need to carefully decide whether a patient should start or continue anti-cancer regimens during the pandemic. They are suggested to divide the cancer patient population into different groups and decide accordingly. Some treatments and care can be postponed or dealt with remotely; others need urgent hospital care. Doctors are trying to find alternatives wherever possible to reduce nosocomial infection. There is another thre at level-the worsening of pulmonary symptoms during lung cancer progression can be similar to that typical of COVID-19.

These similarities can pose a significant challenge for clinicians in distinguishing lung cancer evolution from a potential COVID-19 infection based on radiological and clinical evidence. Importantly, these specific conditions require very different therapeutic approaches (Calabrò etal., 2020) [20].

Anti-CD20 Antibodies Therapy AND B-CELL NHL

Non-Hodgkin Lymphoma (NHL) is a type of cancer that initially affects the white blood cells called lymphocytes. B-cell NHL starts in B lymphocytes. The patient's body starts producing irregular B lymphocytes, and their adaptive immune system takes a hit.

Standard treatment for patients with B-cell non-Hodgkinlymphomas (B-NHL) frequently includes monoclonal anti-CD20 antibodies like rituximab (R) and obinutuzumab (Obi), which target and deplete B-cells for at least 6-9 months. Patients requiringanti-CD2 0therapy are at risk of severe COVID-19 (Gaitzsch et al., 2021, Houot, Levy, Cartron & Armand, 2020) [21, 22]. B-cell depleted lymphoma patients seem to have more extended in-hospital stay, higher risk of re-infection, slow virus shedding, and a high chance of evolution of the virus within them. B-cell depletion can also inhibit the formation of functional memory CD8+T-cells and the maintenance of helper CD4+ T-cells responses (Gaitzsch et al., 2021, Duléry et al., 2021, Hao etal., 2020, Mehta, Porter, Chambers, Isenberg & Reddy, 2020) [21, 23, 24, 25].

However, pausing rituximab therapy in these patients might increase the requirement for corticosteroids, which could worsen outcomes in patients with COVID-19. There are also advantages this therapy offers for COVID patients. COVID-19 associated hyper inflammation, severe lung pathology, etc., can be treated with rituximab. There is a chance that B-cell depleted patients do not have severe COVID-19 illness, but their condition may inhibit or reduce the protective immunity following infection and vaccination. Baker et al. suggested that B-cell depletion is unlikely to influence or be significantly influenced by the significant pathological features in COVID-19. However, B-cells are required for future immunity against the virus (Baker et al., 2020) [26]

BCG and Androgen Deprivation Therapy

Some anti-cancer therapies have been shown to improve outcomes in COVID-19patients. Prostate cancer patients on androgen deprivation therapy (ADT) were four times less likely to get infected than other prostate cancer patients and five times less likely to contract the disease than patients with other cancer types (Montopoli et al., 2020) [27]. Prostate cancer patients undergo ADT to control their tumor progression since dysregulation of androgen and androgen receptor (AR) signaling is associated with prostate cancer (Chakravarty et al., 2020) [28]. The SARS-CoV-2 virus binds to angiotensin-converting enzyme2 (ACE2) for cell entry, and then TMPRSS2 proteolyticallyc leaves the S protein, allowing fusion of viral and cellular membranes. Incidentally, TMPRSS2 is an important gene for primary prostate cancer (Stopsack, Mucci, Antonarakis, Nelson & Kantoff, 2020) [29] and the androgen receptor regulates its transcription. ARs also regulate TMPRSS2 expression in non-prostatic tissues, including the lung. Inhibition ofTMPRSS2 may decrease the severity of SARS-CoV-2 infections. In vitro and in vivo results show that androgen deprivation reduces TMPRSS2 transcription in the murine lung (Montopoli et al., 2020). Androgen can also affect the activity of myeloid cells, dendritic cells, and specific immune subsets that are directly involved in viral clearance (Chakravarty et al., 2020) [28]. Thus, several studies have advocated for the use of anti-androgens and ADT as a potential therapeutic option in COVID-19, suggesting possible protection against SARS-CoV-2infection.

The Bacillus Calmette-Guérin (BCG) vaccine, applied for protection against tuberculosis, exhibits some degrees of cross-immunity against several bacterial and viral

infections. It is also given to prostate cancer patients. Although the BCG vaccine does not directly give coronavirus immunity, it protects against the virus through increased non-specific responses to many pathogens through the action of innate immune cells. The infection rate in patients was lower for those who received recent BCG therapy than those who had received therapy more than a year ago, but this was not statistically significant (Ohadian Moghadam et al., 2021) [30]. Interestingly, nations with mandatory BCG vaccines had low numbers of COVID-19 confirmed cases and reduced mortality. BCG-vaccinated healthy individuals had induced trained immunity, which enhanced the antimicrobial properties, and reduced viral loads, resulting in less inflammation and symptoms (Koneru et al., 2021) [31]. However, WHO declared that there is no evidence that the BCG vaccine can protect against COVID-19, and they are still waiting for clinical trial outcomes.

COVID-19 Vaccine Tolerance in Cancer Patients

Since anti-cancer therapies might affect the patient's immune system, there are worries about the patients' tolerance toward the COVID-19 vaccines. Many groups worldwide checked the safety of different available vaccines in patients undergoing various immunosuppressive treatment/ therapy. For example, Scoccianti et al. Showed that patients who have undergone radio therapy recently (<6 months) are not less tolerant to the Moderna mRNA vaccine and have similar early and late adverse effects as healthy controls (Scoccianti et al., 2021) [32]. Similarly, Chenet al. showed that cancer patients receiving ICI treatment <1 month before vaccination are not at increased risk of developing immune-related adverse effects after Pfizer-BioNTech and Modernam RNA vaccines (Chenetal., 2021) [33]. Waissengrin et al. observed that even in patients with previous immune-related side effects, the Pfizer-BioNTech vaccine-related side effects were either mild or non-existent (Waissengrin, Agbarya, Safadi, Padova & Wolf, 2021) [34].

There have been reports of cases where people have experienced swollen lymph nodes as a side effect of the vaccine (Indini et al., 2021) [35]. This is especially bad if spotted in breast cancer or other cancer patients as it may imitate cancer disease progression. A swollen lymph node under the arm is asign of breast cancer spread, and hence breast cancer patients are recommended to get the vaccine on the arm opposite to the breast cancer ("COVID-19 Vaccines in People with Cancer", 2021) [36].

Anti-Cancer Therapies and COVID-19 Vaccine Efficacy

The vaccine efficacy may not be the same in all individuals, especially in cancer patients. Many studies have shown lower or even no vaccine efficacy in patients undergoing anti-cancer regimens. In comparison with solid tumors, a significantly lower sero conversion rate was observed in patients with hematologic malignancies (85%), especially patients undergoing highly immune suppressive therapies such as anti-CD20 therapies (Agbarya et al., 2021) [37]. After the first vaccination with the BNT162b2 messenger RNA (mRNA) vaccine (BioNTech-Pfizer), Monin-Aldama et al. described rates of seroconversion of 97, 39, and 13% in healthy controls, solid cancer patients, and patients with hematological malignancies, respectively (Monin-Aldama et al., 2021) [38]. Most myeloma patients respond poorly after receiving the first dose of any anti-SARS-CoV-2 vaccination and need booster vaccination (Ghandili et al., 2021) [39]. For solid tumor patients, the anti-spike IgG antibody response to the BNT162b2vaccine was the lowest for patients undergoing immunotherapy plus chemotherapy/ biological therapy (Eliakim-Raz, Massarweh, Stemmer & Stemmer, 2021) [40]. Ehmsen et al. looked for SARS-CoV-2-specific CD8+andCD4+Tcell responses after mRNA vaccination in patients with solid and hematologictumors. They observed that patients with solid cancer generally elicited excellent humoral but insufficient cellular immune responses, and patients with he matologic malignancies rarely elicited adequate humoral and cellular responses after vaccination (Ehmsen et al., 2021) [41].

Studies show that compared to other immune suppressive treatments, patients receiving anti-CD20 antibodies therapy have an increased risk of COVID-9 disease and a 36-fold reduction in humoral responses after the second dose of COVID-19vaccination (Patel et al., 2021, Crombie et al., 2021) [42, 43]. Similarly, long-term CD20 inhibitor users are at higher risk compared to short-term users. Use of anti-B-cell targeting treatment within the previous 12 months and lowCD19+ B-cell numbers (below the standard threshold) were associated with a failure to achieve sero positivity and a low probability of achieving a protective anti-S IgG level after the secondBNT162b2 dose (Malard et al., 2021) [44]. Another study showed that current treatment with BTK inhibitors for CLL (chronic lymphocytic leukemia) is associated with failure to generate sufficient antibody response after the second dose of vaccine (Parry et al., 2021) [45].

Perry et al. showed that the humoral response to the BNT162b2 mRNA COVID-19 vaccine is impaired in patients with B-NHL who are undergoing rituximaborobinutuzumab (R/Obi) treatment. A longer time (about nine months) since exposure to R/Obiis associated with improved response rates to the COVID-19 vaccine. There were also differences depending on thetype of B-NHL: the average time to achieve positive antibody serology was prolonged in patients with indolent B-NHL compared with patients with aggressive B-NHL. This might be due to the longer exposure to monoclonal antibodies or due to the disease type itself (Perryetal., 2021) [46].

The B-cell depletion during or immediately after vaccination affects the generation of B-cell memory and the levels of neutralizing high- affinity antibodies (Duléry et al., 2021) [23].

Vaccination Strategy for Cancer Patients

As immune compromised individuals, cancer patients should be given top priority for vaccination. Live virus vaccines are not recommended to cancer patients because

they can have unwanted side effects ("COVID-19VaccinesinPeoplewithCancer", 2021) [36]. Both vaccines available in India-Covishield, and Covaxin, are safe to use in cancer patients. For patients undergoing anti-cancer therapy using rituximab, vaccination should be delayed to at least six months after completion of therapy if possible, or however long it takes to have absolutely mphocyte count ≥ 1.0 and B cell counts ≥ 50 (Thirumalairaj et al., 2021) [47].

Different vaccine strategies can be followed to increase immunogenicity in cancer patients. The FDA has authorized a third dose of the mRNA vaccines (Pfizer-BioNTech and Moderna) at least four weeks after the second dose, and the CDC recommends this third dose for patients having weakened immune systems ("COVID-19VaccinesinPeoplewithCancer", 2021) [36]. The benefit of an additional booster to improve vaccination response comes from data regarding the seasonal influenza vaccine booster in cancer. Considering that the T immune response could play an essential role in the protective response against SARS-CoV-2, the booster could initiate a T cell immunity response, compensating for the impaired humoral immunity. Patients can also be given one dose of each of two different vaccines after consultation with their doctors (Deming & Lyke, 2021) [48].

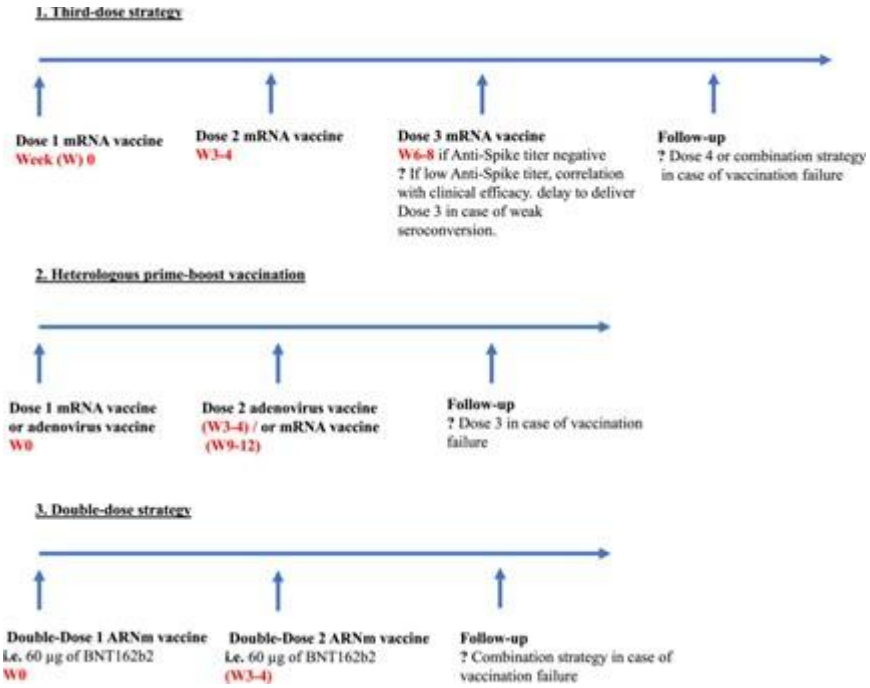

Figure 2: Hypothesised vaccine strategies for cancer patients (Barrière, Re, Peyrade & Carles, 2021) [49]

2. Conclusion and Perspectives

The immunosuppressive effects of different anti-cancer therapies like chemotherapy, radiotherapy, targeted therapy, and immunotherapy do have an impact on the worsening of COVID-19 disease, but only if the patient had undergone very intense therapy cycles just a few weeks (less than 2-4 weeks) before the onset of COVID-19 symptoms. Hematologic tumor patients suffer worse symptoms and disease course than solid tumor patients because of the nature of their tumor and the treatment regimens that inactivate the patient's immune system. However, not all therapies are harmful. BCG vaccination and androgen-deprivation therapy have shown improvement in COVID-19 patients, with lesser disease severity and mortality. Since cancer patients are usually older and have declining health, they need to be given priority for COVID-19 vaccination and further booster doses to improve immunity.

Two years on, there is still a lot unknown regarding the virus and its behavior. Further studies and trials need to be conducted to find the pathways through which various therapies harm COVID patients and how to counteract them effectively. By finding more therapies that show a negative correlation with COVID-19 severity, we can gather more treatment strategies for patients.

3. Limitations

Many studies that observed a correlation between anti-cancer therapy and COVID-19 disease considered small sample sizes or just patients of one hospital and hence contradicted each other. There need to be wide-scale studies in different countries to determine the correlation and other related factors that affect disease severity. Many ongoing trials will add to the information this review covers.

4. Declarations

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Author's Contribution

I Harshitha Vasan, of IISER-Mohali is the first author of the paper. This paper is part of my summer internship project, which was done under the guidance of Ms. Amrita Tiwari. The project study was conducted by Old Dominion University, USA as part of the REYES-SUMMER Program-2021. It is a literature review study that is based on the current COVID19 pandemic & its correlation with cancer.

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