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REVIEW ARTICLE

SARS-Cov-2 infection in cancer patients, susceptibility, outcome and care

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ABSTRACT

The COVID-19 pandemic has led to many problems in cancer patients, which in part are due to insufficient knowledge of the exact implications of the virus on these individuals. Perceptions based on known facts about previous pandemics and coronaviruses might not agree with actual real-life experience and objective findings. We present a compilation of scientific facts and actual observations on different aspects of SARS-CoV-2 infection in cancer patients. These patients are at increased risk of viral contraction and have higher chances of severe disease/mortality. The latter is impacted by other factors and is still debated. In contrast to preliminary impressions, the benefits of anti-cancer treatments outweigh their risks and should be continued. Cancer patients generate antibodies in response to vaccination but in lower amounts than healthy people, especially those with hematologic cancers. Boosters, including third doses, have shown increased immune-responses in most patients. Vaccination should be prioritized in these individuals.

Key indexing terms: Cancer; Vaccines; COVID-19; SARS-CoV-2. **[Am J Med Sci 2022;364(5):511–520.]**

INTRODUCTION

Coronaviruses are single-stranded RNA viruses that infect a variety of mammalian and avian hosts. They have been around for possibly millions of years with the first human coronavirus being isolated in the 1960s. Despite the history of previous outbreaks like MERS and SARS caused by members of this family [1,2] the SARS-CoV-2 betacoronavirus was not adequately contained and led to the COVID-19 pandemic causing 6,261,708 deaths worldwide as of May 13, 2022.[3] The novelty of the strain with many unknown factors related to its infectivity, host susceptibility, genetic variabilities, etc., is in part responsible for this crisis.

Host immunity has a major role in infection control and is involved in the severeness of COVID-19 outcome. It also contributes to tumorigenesis in cancer patients since neoplastic cells need to escape the antitumor immune response and to do so, they suppress the immune system, reprogram immune cells to become pro-cancer and/or secrete pro-tumor factors. Therefore, a difference in the response of cancer patients to SARS-CoV-2 infection compared to people without cancer, is plausible.[4]

It has been suggested that elderly individuals and those with comorbidities like cancer are at risk of severe disease and worse prognosis, requiring more attention and care. A large number of cancer patients need constant visits to treatment centers for disease management or observation and monitoring. Their immunosuppressed state due to the disease itself or anticancer therapy, might place them in a vulnerable state for contracting infections.[5] However, judgements based on existing information related to former pandemics and coronaviruses might not inevitably agree with actual real-life facts and objective findings. We herein present a compilation of the scientific evidence and actual observations/clinical evidence on different aspects of SARS-CoV-2 infection in cancer patients and accordingly, offer suggestions to provide the best care for these patients during the COVID-19 pandemic.

THE RISKS OF COVID-19 IN CANCER PATIENTS

The dangers related to COVID-19 in cancer patients can be explored from different angles: are they more susceptible to contract SARS-CoV-2 infection? Are they at risk of more severe disease and is mortality higher in these individuals? How does anticancer treatment affect them? For each of these questions we first examine the established scientific facts and then discuss the clinical data and actual observations of researchers extracted from studies with larger sample-sizes and/or cohorts of cancer patients with RT-PCR-confirmed COVID-19. Finally, closing statements are provided that supply evidence-based suggestions for maximum patient support.

SUSCEPTIBILITY OF CANCER PATIENTS TO COVID-19

Various factors have been proposed to be involved in contraction of SARS-CoV-2 including genetics,[6] sex-

hormones,[6-10] immune status,[10] co-morbidities etc. Age, a compromised immune system and the general vulnerability of cancer patients to viral infections [11] are among the most argued justifications of increased susceptibility of this group to COVID-19.[10-13]

Facts

COVID-19 causes disruption in the balance of the immune system and undermines inflammatory reactions.[14] Increased age and immunosuppression, either as a consequence of the disease or due to anticancer treatments, are common characteristics of cancer patients and both are also known to contribute to a greater risk of COVID-19 infection.[10] Aging, is associated with elevated levels of IL-6, which has been shown to promote viral replication and induce pulmonary injury. This cytokine is also upregulated in COVID-19 and cancer.[12-16]

An interesting study by Kwan et al [17] reported increased RNA expression of viral-entry-genes such as angiotensin-converting enzyme-2 (ACE2), transmembrane protease serine-2 (TMPRSS2), and cathepsin-L in different cancers, leading to increased susceptibility of cancer patients. Others have also reported the existence of ACE2 mRNA in almost all cancers.[18]

During cell entry, S1 and S2 subunits of the SARS-CoV-2 spike protein attach and fuse to the ACE2 receptors on target cells and undergo protease cleavage,[19] mainly by the TMPRSS2 cleaving enzyme. Cathepsin can also perform this task in ACE2-expressing cells that lack TMPRSS2. The end result is fusion of host- and viral-membranes leading to viral cell-entry.[20] Upon entry, SARS-CoV-2 replicates, releases its particles and causes pyroptosis followed by secretion of numerous factors including cytokines and chemokines which can ultimately attract innate immune cells.[21] These cells, specifically effector T-lymphocytes, are responsible for eliminating virus-infected host cells.[22] On the other hand, these same lymphocytes normally recognize tumor-associated antigens expressed on tumor cells and destroy them. However, the tumor microenvironment fights this antineoplastic immune response by reducing the number and function of T-cells,[13] which is further attenuated by chemotherapy, steroids and radiotherapy.[22] Therefore, the ability of cancer patients to combat viruses under such circumstances is reduced, making these individuals more prone to SARS-CoV-2 infection.

Observations and clinical evidence

The observations made in various studies generally support the above-mentioned facts. Epidemiologic reports based on screening results have mostly shown an increased susceptibility of cancer patients to SARS-CoV-2 infection, despite their reduced chance of exposure due to lower social and daily activities.[23] However, not all were in agreement.

Using electronic health records of 73,449,510 patients in the US, Wang et al [24] reported 16,570 individuals with COVID-19, of whom 1200 had cancer and 690 had a recent diagnosis within the past year. After adjusting for risk-factors of COVID-19, they found an increased risk of SARS-CoV-2 infection for cancer patients with higher chances in those diagnosed within the past year, African-Americans, and individuals with leukemia, non-Hodgkin's lymphoma and lung cancer. Age and gender had no impact on susceptibility to infection but an increased risk was found in women with colorectal cancer and non-Hodgkin's lymphoma. In another study, of 72,314 (62% confirmed cases) [10-25] Chinese COVID-19 patients, 0.5% had cancer, which was higher than the 0.29% overall cancer incidence in the Chinese population.[26] In a systematic review/meta-analysis, compilation of 62,000 COVID-19 patients from 14 studies performed in different countries, reported a 6% cancer incidence, which was much higher than the 0.2% of the general population. The highest and lowest incidence were found in Spain (17.296%) and China (0.514%), respectively.[27] By evaluating 9280 patients from 68 hospitals in Italy, it was concluded that cancer patients were at greater risk of SARS-CoV-2 infection in comparison to those without cancer.[9] A meta-analysis of 7049 Chinese COVID-19 patients reported an association between cancer and risk of infection.[23] Another meta-analysis evaluated the prevalence of eight comorbidities among 12526 COVID-19 Chinese patients and found cancer to be one of the underlying diseases that had a higher prevalence among the study group as compared to the general population.[28]

Conversely, an increased risk of positivity for SARS-CoV-2 has not been reported in thyroid cancer [29] and pediatric patients (small sample-size).[30] Additionally, the cumulative risk of COVID-19 during a 5-month study period in Norway was reported to be similar between cancer and non-cancer patients after adjusting for age, and there was an increased risk in patients with leukemia, lymphoma and endocrine tumors, but not in those with lung cancer.[31] Also, a French study found similar SARS-CoV-2 infection rates between cancer patients and the global population.[32] A nation-wide study in Korea evaluated the risk factors for SARS-CoV-2 infection in 7333 positive cases and showed that cancer actually reduced the risk for infection.[33] A lower risk of positive testing was also reported [34] in a study on data from a multi-ethnic cohort of 20,899 patients tested for COVID-19 at Mount Sinai (USA).

Concluding remarks

Based on the large number of studies in support of an increased probability of cancer patients contracting SARS-CoV-2 infection, it seems that these individuals are more susceptible to the virus. However, we can't dismiss the contradicting studies and propose further continent-wide epidemiologic analyses of this issue.

COVID-19 DISEASE SEVERITY AND MORTALITY IN CANCER PATIENTS

Considering the limited hospital facilities and ongoing peaks in many countries, prioritization of hospital admittance is vital. If cancer patients have a higher likelihood of morbidity and mortality, they should receive selective hospitalization.

Facts

The cytokine storm brought about by increased levels of cytokines, especially IL-6, is the most serious and deadliest outcome of COVID-19.[19] It is a hyper-immune reaction and can develop in response to underlying issues like cancer, leading to a more severe outcome. Additionally, the already elevated serum IL-6 of cancer patients confounds the upregulation of this cytokine brought about by SARS-CoV-2 infection, resulting in increased risk of disease severity and cytokine storm. Furthermore, IL-6 causes tumor progression,[12] which could raise the reverse probability, i.e., increased IL-6 resulting from COVID-19 may exacerbate the malignancy. Generally speaking, underlying augmented inflammation and deregulated immunity due to cancer and/or aging, support an increase in pro-inflammatory cytokines and lead to severe COVID-19.[35] This could indicate an added risk for older cancer patients, which is why age has been considered as a factor in epidemiologic researches presented below.

SARS-CoV-2 infection causes major modifications in the number and function of T-cells and produces progressive lymphopenia resulting in 95% reduction of total T-cell counts in the severe stages of the disease. This would contribute to the already existing exhausted T-cells present in many cancers, leading to exacerbation of COVID-19 outcome.[13] Indeed lower lymphocyte-count has been reported in severe COVID-19 cases.[36]

It may be hypothesized that immune response in various malignancies and in different cancer grades might have different effects on viral infections including SARS-CoV-2. For example, dense lymphocytic infiltration adjacent to neoplastic tissues of oral squamous cell carcinoma has a protective effect and lowers the histopathologic grade,[37,38] which is in contrast to breast cancer that shows worse prognosis in increased inflammatory infiltrates.[39,40]

ACE2, receptors for SARS-Cov and SARS-CoV-2, are upregulated in many cancers. An increase in these receptors has been shown to be associated with more severe disease and greater fatality in SARS-Cov infected mice.[35]

Androgen receptors regulate the transcription of TMPRSS2 in prostate cancer as well as non-prostatic and noncancerous tissues like the lung. They also alter the immune response by increasing neutrophil number/function and cytokines and also reduce antibody reaction to viral infections. Therefore, an expected finding would be an increase in disease severity and mortality in men, especially those with prostate cancer. However, it has been shown that COVID-19 severity was increased in men, regardless of the cancer type.[9]

In general, factors in common between cancer and COVID-19 like lymphopenia, T-cell exhaustion, etc., which mainly cause immune dysregulation, put cancer patients in a disadvantage compared to non-cancer individuals and they basically have less means to defend and eradicate the infection, leading to more severe outcomes.

Observations and clinical evidence

A large number of studies/meta-analyses have reported increased disease severity and/or mortality in COVID-19 patients with cancer.[23-36,41-48] But not all data support this observation that cancer per se increases COVID-19 mortality.[31-50]

Increased age is one of the most investigated factors in cancer-COVID-19 patients with the majority agreeing to its significant effect on mortality and/or severe outcome.[41-43,45-52] Conversely, in a study on SARS-CoV-2-infected individuals in New York, cancer patients older than 51 years demonstrated a non-significant lower mortality rate than non-cancer patients and those younger than 50 years had a significantly higher mortality rate in comparison. In the same study, intubation risk significantly increased only in the 66–80-year-old cancer patients and not in the other age strata.[50]

Another debated factor is male gender, which has been suggested to increase mortality in cancer-COVID-19 patients in some studies,[9-51] but not others.[31-42]

Race has been variable among studies. In a large investigation on 73.4 million patients, African-Americans with cancer were reported to have an increased risk of infection compared to whites. Also African-Americans with cancer and COVID-19 showed worse outcomes like hospitalization, but not death.[24] Among cancer patients with confirmed SARS-CoV-2 infection, Asian ethnicity was associated with increased disease-related mortality, compared to the white population.[53] In real-world data analysis of 146,702 cancer patients, non-Hispanic black and Hispanic/Latino individuals did not have increased fatality rates compared to non-Hispanic whites, but a combination of Asian/Native Hawaiian/Pacific Islander, other or unknown race/ethnicities demonstrated reduced mortality.[45] Also based on an analysis of the COVID-19 and Cancer Consortium (CCC19), non-Hispanic black and Hispanic ethnicities showed more severe COVID-19 symptoms and higher 30-day mortality rates for non-Hispanic Blacks, but not for Hispanics.[46] Non-white race emerged as a risk factor for hospitalization in a study on New York patients.[52] Other studies did not find racial/ethnic associations with death among cancer-COVID-19 individuals.[41-43]

Cancer type has been widely investigated with special attention given to hematologic malignancies, the reason being reduction in myeloid and lymphoid cells that can lead to increased predisposition to cytokine-mediated

inflammation. Higher mortality/severe outcome due to COVID-19 in patients with hematologic cancer was reported by some [42-52] while others have indicated lung cancer [27-47] melanoma, uterine, and kidney cancer [42] to be associated with greater risks. Fu et al [44] reported hematologic cancers to have the highest mortality-rate among active cancers, but its comparison to solid malignancies in multivariable analysis did not achieve significance. Others have not found correlation between cancer type and increased severity/mortality [31-45] or difference in outcome between hematologic and solid cancers.[49]

Comorbidities are another widely investigated factor. Mortality rate was shown to increase in cancer-COVID-19 patients with the number of comorbidities (two versus none), but not with obesity status.[41] Hypertension and/or chronic kidney disease and history of cardiac disorder were associated with severe outcomes, but did not reach statistical significance in multivariate-analysis.[52] In a cohort of cancer-COVID-19 patients, cardiovascular and pulmonary comorbidities showed correlation with higher disease severity.[46] In another study, multivariate analysis showed that history of pulmonary circulatory disorder was significantly associated with death in cancer-COVID-19 patients.[45] Other investigations have shown significant relationships between fatality and multiple comorbidities [43] and obesity.[49]

Additional factors correlated with death/severe outcome in cancer patients with SARS-CoV-2 infection include active cancer,[41-45] a number of laboratory values,[43,44] and distant metastasis in some cancer types.[31-42] Mehta et al [43] and Robilotti et al [52] did not report metastasis as a significant factor in cancer-COVID-19 patients.

An interesting observation about immune dysregulation was that COVID-19 patients with similar immunological indices had the same prognosis, irrespective of cancer. The association of mortality with severe immune dysregulation was stronger than that with cancer. The reason for increased death among SARS-CoV-2 infected patients with cancer compared to those without cancer was suggested to be the significantly lower immune cell-count and higher inflammation in the former.[36]

Concluding remarks

It seems that cancer patients infected with SARS-CoV-2 are at increased risk of disease severity/mortality, which mostly increases in men, non-whites, those with additional comorbidities and hematologic cancers. However, there are some recent large studies that dispute this fact and the factors affecting outcome are still being debated.

THE EFFECT OF ANTICANCER THERAPY ON COVID-19

Anti-cancer treatments include those with cytotoxic effects like chemo- and radio-therapy and non-cytotoxic treatments such as hormone- and immune-therapies. Considering their importance in improving patient survival, it is paramount to weigh their benefit against the risk of SARS-CoV-2 infection.

Facts

Chemotherapy suppresses the bone marrow and causes thrombocytopenia, neutropenia and lymphopenia leading to increased susceptibility to infections, including SARS-CoV-2. Also, the resulting lymphopenia sets the patient at a weaker state to fight the virus, which becomes more pronounced when the COVID-19-related lymphopenia is added to the situation, ultimately leading to more severe disease. Similarly, radiation induces lymphopenia as a result of direct exposure of lymphocytes to the radiation, with increased risks in proton beam therapy, stereotactic body radiation, or a hypofraction schedule.[54]

On the contrary, the effects of immunotherapies are not as clear-cut. Immune checkpoint inhibitors have become one of the most debated treatment strategies of this group in the COVID-19 era, with both advantageous and harmful effects for SARS-CoV-2 infection. On one hand by increasing T-lymphocyte response, immune checkpoint inhibitors reduce infection rate and viral replication leading to decreased infectivity and disease severity; on the other hand, they may augment inflammatory responses, resulting in enhanced signaling of the interferon pathway, especially type II interferons, which can end in excessive immune response with outcomes like ARDS and cytokine storm.[55] Considering the disease course of COVID-19, immune therapy might be beneficial in the initial stages of the disease to help fight the virus. However, in progressed and severe stages, an increased immune response may become aligned with the development of a cytokine storm and act in conjunction, leading to worse symptoms. Therefore, a time-dependent role for immunotherapy has been suggested, which should be considered before administration.[56]

Hormone-therapies have been discussed to a lesser degree. Androgens, in addition to increasing interleukin production and reducing antibody response to viruses, have a regulatory role on TMPRSS2 expression in pulmonary tissues and prostate cancer and their blockage as a treatment for the latter has been hypothesized to protect against SARS-CoV-2 infection. On the other hand, estrogens exert a protective role against infections and in the case of SARS-CoV-2, factors like immune-modulation and reduction of ACE2 expression by estrogen along with X-linked genes associated with inflammatory responses lead to decreased vulnerability against COVID-19 and less severe symptoms.[8-10] Therefore their inhibition in ER positive breast cancer by tamoxifen has been hypothesized to increase the risk of COVID-19.[57] However, others suggest some of the features of Tamoxifen to be protective against SARS-CoV-2 and COVID-19. These include its anti-androgen effect, its Sig-R

ligand-related activities resulting in early viral replication inhibition, and its blocking protease associated membrane fusion.[58]

Observations and clinical evidence

Several studies have been in favor of continuing anticancer therapies with close patient monitoring, despite the pandemic situation. When adjusted for relevant factors, anti-cancer treatments in general had no significant effect on mortality/severity of COVID-19.[32-53] In agreement, a large multicenter study on nearly 60,000 patients under anti-cancer therapy showed a low SARS-CoV-2 infection rate among these patients,[59] the results of which was confirmed in another smaller study.[60]

An important point is to separate toxic and non-toxic anti-cancer treatments, i.e., chemo- vs. immune/endocrine-therapy. Some investigations support an increased COVID-19 severity and/or fatality in recipients of both therapies,[45] while others only found treatment with immune checkpoint inhibitors alone [52] or chemotherapy alone [46-56] to be correlated with severe COVID-19 outcomes. In a large study in Norway, recent cancer treatment had no effect on age and sex-adjusted fatality, but anticancer therapy in the past three months led to increased risk of the combined outcome 'death and/or hospital admittance due to COVID-19'.[31]

Regarding hormone-therapies, Italian researchers have shown that androgen deprivation therapies in prostate cancer patients have a partial protective effect against SARS-CoV-2 infection and complication, in line with androgen receptor features.[9] However, they indicated estrogen ablation to reduce COVID-19 incidence in breast cancer patients.[61] In confirmation, Bravaccini et al [58] demonstrated a protective role of the selective estrogen receptor modulator Tamoxifen, which was in contrast to the opinion of some,[57-62] but not others who suggest that this drug directly suppresses androgen receptor signaling, hence counteracts SARS-CoV-2.[63] Grivas et al [46] did not find increased severity of COVID-19 following endocrine therapy.

Concluding remarks

According to the reviewed studies, it seems that the benefits of continuing anticancer therapy, outweighs its risks. However, considering the vulnerable state of these patients, a case-by-case approach and multidisciplinary management with close teamwork would be beneficial.

VACCINATION IN CANCER PATIENTS

Vaccines against SARS-CoV-2 have been developed with different technologies including mRNA (Pfizer/BioNTech, Moderna), adenovirus vector (AstraZeneca/Oxford, J&J), inactivated SARS-CoV-2 (Sinovac, Bharat Biotech, Sinopharm) and protein subunit (Vector Institute, Anhui Zhifei Longcom Biopharmaceutical).[64] There are currently 184 vaccines in pre-clinical phases and a total of 17 have been offered to the general population.[65] Cancer patients were excluded from registration trials in the five vaccines approved for use by USFDA and European Medicines Agencies. Therefore, the information generated in the past months of vaccine rollout is extremely limited. A prospective, national, multicenter, longitudinal, multi-cohort study is being conducted in the Netherlands on individuals receiving active anticancer treatments against solid tumors with the objective of clarifying issues like vaccination outcome in different anticancer treatment types.[66]

An interim analysis of a prospective observational investigation on 34 healthy individuals and 56 solid and 44 hematologic cancer patients showed BNT162b2 to be well tolerated among the participants. There was only one potentially life-threatening event in a patient with a former check-point inhibitor administration. Inadequate effectiveness of a single dose of the vaccine was reported on day 21 of inoculation, which significantly improved 2-weeks after the booster dose in solid cancer patients, according to anti-S IgG tests. The number of individuals with hematologic cancer was limited; however, based on the available data, 60% of these patients were seropositive after the second dose compared to the 11% who did not receive the booster.[67] Other studies have reported similar findings:

A 39.5% response-rate was reported in chronic lymphocytic leukemia patients following two doses of BNT162b2, which decreased to 16% in those on active treatment and was dependent upon type of treatment, age, sex and immunoglobulin levels. Compared to the healthy controls, the difference in antibody response was significant.[68] Similarly, seroconversion following SARS-CoV-2 infection in cancer patients was reported to be 94.5% in those with solid tumors and approximately 82% in individuals with hematologic malignancies, which was similarly dependent on treatment.[69] Also, 90% of 102 solid cancer patients on active IV therapy, demonstrated sufficient response rates to BNT162b2, but significantly lower than the 78 healthy controls. Chemotherapy+immunotherapy was reported as being associated with lower response in multivariate-analysis.[70] Previous SARS-CoV-2 infection of cancer patients was shown to induce high S-IgG levels after a single-dose of BNT162b2 and was higher than those without previous infection. Immunity increased significantly in the latter after the second dose injected on day 21.[71] A seroconversion rate of 94% was reported in solid cancer patients, 3-4 weeks after the second dose of BNT162b2 with significantly lower anti-spike levels compared to healthy controls.[72]

According to Ehmsen et al., cancer patients demonstrated insufficient immune response after 2 doses of mRNA vaccination with rapid reduction of anti-S IgG within the first 3 months, necessitating a third booster. Further follow-up showed significantly higher anti-S IgG in solid tumors compared to hematologic cancers after 36 days. Decline in both groups was reported gradually

to the 6th month, after which the patients received a third dose resulting in anti-S IgG rises after 39 days, measured to be 2-5-fold higher than the second inoculation. Both cancer types showed sufficient antibody response after the 3rd booster, with better results observed in the solid tumor group. Active anticancer therapy during vaccination, negatively affected seroconversion in hematologic cancer patients.[73] In agreement, following analysis of IgG against SARS-CoV-2 RBD antigen in a large-scale study, 3rd dose administration of BNT162b2 was shown to induce a significant increase in immune response, suggesting efficient formation of memory B-cells. An exception was reported in receivers of rituximab treatments, which are known to reduce these cell types.[74] In another study, BNT162b2 mRNA vaccination led to increased neutralizing antibodies in 67% of solid cancer patients undergoing cytotoxic anti-cancer therapy followed by 3-fold increases after the 2nd dose, which was considerable, but less than the amount of that in healthy controls. One week after 3rd-dose administration, neutralizing antibody and B-cell- but not T-cell-responses increased significantly.[75] Serologic monitoring based on anti-spike antibody titers was suggested as a means to help schedule the appropriate time for the 3rd booster dose in cancer patients.[76] Third BNT162b2 boosters were evaluated in patients with a variety of lymphoid cancers and the results showed increased T-cell response in nearly all patients, which was more in those who were seropositive after the 2nd and 3rd doses. These individuals had increased anti-S after their 3rd inoculations. Patients who were seronegative after the 2nd dose remained so following their 3rd boosters. However, the elicited immune response in at least some of these patients supports vaccination, even in cancer patients who show vaccine failure.[77]

Adverse events that can impact cancer patients include thrombosis associated with thrombocytopenia [78] and lymphadenopathy near the injection site which has raised concern for misdiagnosis of metastasis in fluorodeoxyglucose PET/CT and ultrasound of patients with skin cancer [79] and oncologic imaging and screening of patients.[80]

Due to the enhanced permeation and retention phenomenon, it has been suggested that until large-scale studies have been conducted to determine the appropriate dose and the effects of liposomal vaccines on the biologic behavior of tumors, administration of vaccines using other technologies (non-liposomal) should be considered for patients with solid neoplasms.[81]

Concluding remarks

Based on current knowledge, immune response to vaccination in cancer patients seems to be lower than healthy individuals.[78] To optimize the benefits of vaccination in these patients and prevent misdiagnosis of disease or recurrence/metastasis, it is suggested that inoculations be administered at the farthest point from the underlying cancer as possible [79] and be given at a time when the immune system is minimally affected by anticancer treatment, ideally two weeks before treatment.[64] Delaying administration of the second dose should be avoided so that patients that are prone to having inferior responses to a single dose of BNT162b2 do not become infected in this time span.[78] Third booster doses can increase immune response and are more effective in solid tumors than hematologic malignancies.[82] Considering that some patients do not develop serologic responses even after 3rd booster doses, other strategies should be developed to protect these vulnerable group of individuals.[83]The exact effect of cancer type and anticancer treatment regimen on immune response to vaccination in addition to the appropriate vaccination dose of cancer patients i.e., receiving an increased dose and/or additional booster, needs to be clarified by future research.

PATIENT CARE

General guidelines have been introduced by researchers and clinicians that cover all aspects of dealing with cancer patients during the pandemic.

Cancer patients without established COVID-19

The main management-strategy should be to limit outpatient visits as much as possible or to conduct them through virtual means, where feasible.[5-84]

Remote contact needs to be maintained from 72h before appointments to determine whether the patient suffers from one or more COVID-related symptoms like sore-throat, shortness of breath, cough, fever, bodyache or sudden onset of hyposmia/anosmia and/or dysgeusia. Contact with SARS-CoV-2+ or suspicious or high-risk individuals or hospitalization within the past 14-days should be questioned and the patient be requested to report any situation changes, up until leaving for the appointment.[84]

Upon arrival at the clinic, the same questions should be repeated in addition to performing a temperature-check with observance of all infection-control measures. This initial screening must be recorded and carried out in an area that allows 6-feet distancing and is separate from the examination/treatment room. Appointment numbers should be kept to a minimum to avoid contact between patients in the waiting-room, which should be equipped with proper ventilation and spacing. However, waiting in parking lots or being dropped off at exact appointment time through mobile contact is preferable.

All units providing routine treatments should be kept active and treatments may continue as long as the risk is considered minimal by the oncologist.[84] Hospital visits for anticancer therapies should also be kept to a minimum and every effort be made to avoid complications resulting from chemo/radio/immunotherapy.[85]

TABLE 1. Main points extracted from supportive and opposing studies which were reviewed up to the date of submission.

Critical Points	Studies in agreement	Opposing studies	Suggestions
Large studies support increased susceptibility of cancer patients to contract COVID-19, some offering molecular evidence	9,10,17,18,23-28: No. of patients between 7049 & 72,314	29[*],30[*],31[$],32,33[#],34[#]: No. of patients between 178 & 20,899	Specification of subgroups with the highest risk (e.g. based on race, cancer type, time from diagnosis, etc.
Increased age of cancer+COVID-19 patients is associated with increased mortality &/or severe outcome	41-43,45,46,51,52	50	These patient groups could be prioritized to receive treatment in emergency situations
Male cancer+COVID-19 patients are at increased risk of severe disease	9,41,44,45,46,51	31,34,42	
Anti-cancer treatments[@] do not significantly increase mortality/ severity of COVID-19 & can even have low infection rates	32,41,44,47,79,51,53,59,60	45,46,52,56	Cancer treatments should be continued during the pandemic, preferably using a case-by-case approach, depending on patient condition, cancer, treatment, & vaccination status
Debate on the effect of race on COVID-19 severity in cancer patients continues: non-whites might be more susceptible.	Positive effect of race on severity: 24,44[$],46,52,53	No effect or reduction in severity: 41,43,45	Further studies required
Debate on the effect of cancer type on COVID-19 severity in cancer patients continues	Hematologic cancer has worse outcome: 42,43,46,47,52	31,45,49	
	Lung cancer has worse outcome: 27,47		
	Melanoma, uterine & kidney cancer have worse outcome: 42		
Debate on the effect of hormone-therapy on COVID-19 severity in cancer patients continues	Androgen/Estrogen deprivation & Tamoxifen are partially protective: 9,58,63	46,57,62	Anti-cancer therapy has more benefits than risks and should be continued during the pandemic, but a case-by-case approach is recommended
Vaccination data[^]			
Cancer patients have generally lower responses to vaccines compared to health individuals			
Solid cancers respond better to vaccines compared to hematologic malignancies			
Anticancer therapy impacts vaccine responses; therefore, vaccination would be more effective when the immune system is less affected by these treatments, i.e., 2 weeks prior to therapy			
Advanced age, certain cancer types like hematological malignancies and treatments causing B-cell depletion or those negatively affecting the immune system can result in less effective immune responses after vaccination			
Boosters should be administered in a timely manner with minimal delay to prevent infection in cancer patients since they are already at a disadvantage regarding immune response & antibody levels			
Third boosters increase immunity and can be beneficial even in seronegative patients			
Regarding the general benefits of vaccination in cancer patients, prioritization should be considered in vaccination schedules for these individuals			

[*] These studies have either reported on specific cancer types or used a small sample size
[#] These studies showed decreased chance of infection in cancer patients
[$] In multivariable analysis, hematologic cancers did not have significantly increased mortality compared to solid malignancies, but had the highest mortality among active cancers
[@] These include toxic and non-toxic therapies. The specifics of studies on one or both types have been stated in full within the text
[^] Considering that vaccination in cancer+COVID-19 patients is still being widely investigated, studies have mostly been supportive and their conclusions are presented without stating opposing studies, if any

Cancer patients with COVID-19

All infection control measures should be followed similar to those described above. An additional consideration in these patients is whether or not to administer anti-cancer therapy and/or ICIs. More-recent evidence suggests that the former affects neither severity nor mortality of COVID-19 [51-86] and according to some studies the latter could actually be beneficial.[55-87] However, considering some dispute these reports,[48] it is recommended that each patient be evaluated separately and decisions be made on an individual basis.

LIMITATIONS

Considering the evolving nature and substantial amount of information on COVID-19 and the ongoing pandemic, the gathered data reported in the current review can only represent a snapshot of the events that have occurred at a certain point of time. The conclusions may be modified as new data is published in future large multicenter studies. Data on the different effects and benefits of vaccination in cancer patients is still unfolding and definitive conclusions cannot be drawn. A systematic review and meta-analysis could provide a higher level of evidence on the cancer+COVID-19 topic.

SUMMARY

The immune system in cancer patients acts differently from that in healthy individuals and therefore may process viral infections differently, leading to variations in clinical outcome. Based on current knowledge, cancer patients are more susceptible to contraction of SARS-CoV-2. Most studies find COVID-19 to be either more severe or cause increased mortality, which is further dependent upon increased-age, male gender, comorbidities and some disease-related factors. However, more recent studies are showing similar outcomes in severity and fatality between cancer and healthy individuals. Nevertheless, in order to practice caution at this time, it is suggested that cancer patients who acquire COVID-19, be prioritized for hospitalization in areas where there is shortage of hospital facilities to decrease the risk of possible severe symptoms or death. In contrast to previous perception, anti-cancer treatments do not impose a large risk for these patients and should be continued. Non-attenuated live virus vaccines are considered safe for cancer patients and they should be prioritized to receive all doses at the recommended time intervals, without in-between delays. The reason is that cancer patients can have a lower antibody response compared to healthy people, especially after the first dose and in those with hematologic cancers. Dose modification in these patients either as an additional booster or increased doses at each delivery, requires clarification in future studies. Until eradication of the infection, cancer patients and their professional and non-profession caregivers should be prioritized for vaccination. Table 1 summarizes the main points extracted from the reviewed studies.

CONCLUSIONS

Based on the presented facts and clinical evidence, it is important to enforce rigorous infection-control measures, strictly adhere to cancer-care guidelines, continue anticancer treatments, prioritize hospitalization of cancer-COVID-19 patients and give precedence to vaccination, including booster doses, in individuals with cancer. Further studies regarding an additional booster dose or changes in vaccine titers for cancer patients is essential.

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CONFLICT OF INTEREST STATEMENT

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CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

SE and MA: conceptualization, data curation, investigation, project administration, writing – review and editing, formal analysis.

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