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REVIEW ARTICLE

Immune mechanisms in cancer patients that lead to poor outcomes of SARS-CoV-2 infection



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Patients with cancers have been severely affected by the COVID-19 pandemic. This is highlighted by the adverse outcomes in cancer patients with COVID-19 as well as by the impact of the COVID-19 pandemic on cancer care. Patients with cancer constitute a heterogeneous population that exhibits distinct mechanisms of immune dysfunction, associated with distinct systemic features of hot (T-cell-inflamed/infiltrated) and cold (Non-T-cell-inflamed and/or infiltrated) tumors. The former show hyper immune activated cells and a highly inflammatory environment while, contrastingly, the latter show the profile of a senescent and/or quiescent immune system. Thus, the evolution of SARS-CoV-2 infection in different types of cancers can show distinct trajectories which could lead to a variety of clinical and pathophysiological outcomes. The altered immunological environment including cytokines that characterizes hot and cold tumors will lead to different mechanisms of immune dysfunction, which will result in downstream effects on the course of SARS-CoV-2 infection. This review will focus on defining the known contributions of soluble pro- and anti-inflammatory mediators on immune function including altered T-cells and B-cells responses and as well on how these factors modulate the expression of SARS-CoV-2 receptor ACE2, TMPRSS2 expression, and lymph node fibrosis in cancer patients. We will propose immune mechanisms that underlie the distinct courses of SARS-CoV-2 infection in cancer patients and impact on the success of immune based therapies that have significantly improved cancer outcomes. Better understanding of the immune mechanisms prevalent in cancer patients that are associated to the outcomes of SARS-CoV-2 infection will help to identify the high-risk cancer patients and develop immune-based approaches to prevent significant adverse outcomes by targeting these pathways. (*Translational Research 2022; 241:83–95*)

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has at present, (November 2021) caused 257 million infections and more than 5.1 million deaths worldwide (New York Times, November 21, 2021). Studies have shown that, cancer patients are particularly more susceptible to SARS-CoV-2 infections (0.9% vs 0.29%).¹⁻⁵ Besides that, the factors that have been most consistently linked with increased risk of severe COVID-19 disease and/or death are prevalent in cancer patients, and include but not limited to older age (≥ 60 years), a history of smoking, obesity, hypertension, cardiovascular disease, and diabetes.¹ Higher susceptibility of cancer patients to SARS-CoV-2 infection is either due to impaired immune responses that are characteristic of the cancer (and associated co-morbidities) or due to the anti-cancer treatments that alter immune homeostasis.¹⁻³ To understand why cancer patients are at greater risk of complications and/or death associated with COVID-19 it is important to decipher immune responses that govern the development of specific cancers, associated therapies and comorbidities.^{6,7}

The severity of COVID-19 disease in cancer patients is partly a function of the etiology, type (hot vs cold tumors, where hot tumors have an immunologically active microenvironment), stage and anatomical location of the tumor.^{4,8-12} These factors along with treatment regimens play a crucial role in diversifying the immune landscape of a malignancy.^{8,12} Indeed, it has been observed that COVID-19 patients with hot tumors (ie, lung cancer and hematological malignancies (HM)) are likely to develop severe COVID-19 disease.^{1,4,10,11} Recent reports have shown that adverse outcomes in COVID-19 infected cancer patients can result from: alterations in expression of host proteins that promote SARS-CoV-2 entry (ACE2 and TMPRSS2), an aberrant cytokine profile (mainly IL-1 β , IL-2, IL-6, GM-CSF, IFN γ , TNF- α , and TGF- β), lymph node thrombosis, impaired T/B-cell responses, and impaired inflammasome response – especially the NLRP3 inflammasome.^{1,3,8,13-22} To decipher the mechanisms that drive these adverse outcomes in COVID-19 infected cancer patients, this review will assess the impact of “hot” vs “cold” immune and/or tumor environments (and associated therapies) on susceptibility and course of disease in subjects with these 2 types of tumors and infected with SARS-CoV-2. The mechanisms discussed below can help further research into the development of tailored approaches that promote anti-cancer responses while restraining COVID-19 disease severity.

COVID-19 AND ITS OUTCOMES

Coronaviruses are a diverse group of respiratory viruses that can infect humans and animals.²³ In 2019, Wuhan (China) saw the emergence of a novel coronavirus “SARS-CoV-2” that has been responsible for an unusual and highly transmissible viral pneumonia pandemic that was designated as coronavirus disease 2019 (COVID-19).²⁴ SARS-CoV-2 enters the host respiratory epithelial cells by binding the angiotensin converting enzyme II (ACE2).^{25,26} Specifically, the C-terminal domain of the SARS-CoV-2 spike (S) protein, known as “receptor binding domain (RBD)”, binds ACE2 to aid viral entry into the host cell.^{27,28} Next, host proteases (Transmembrane Protease Serine Protease 2 (TMPRSS2), cathepsin L and furin), cleave the S protein of SARS-CoV-2 that is required to activate endocytic entry of SARS-CoV-2 and initiate infection.^{26,29,30} During the initial phase of the infection, susceptible epithelial cells in the nostrils allow for SARS-CoV-2 replication and subsequent transmission to lower respiratory tract epithelial cells and finally to alveolar epithelial cells (Fig 1).³⁰ Rapid replication of SARS-CoV-2 in the respiratory tract can promote systemic proinflammatory cytokine production (known as the “Cytokine storm”), such as: IL-1 β , IL-6, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN- γ , IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, TNF- α , and VEGF, which subsequently results in dysregulation of immune functions, severe inflammation (including myocarditis) and multiple organ failure in some COVID-19 patients (Fig 1).^{21,22,31-34} The most striking impact of this storm is observed in the respiratory tract, where pro-inflammatory cytokines drive the pathology of acute respiratory distress syndrome (ARDS) and ultimately respiratory failure - the main causes of death in COVID-19 patients.^{11,32,33,35}

SARS-COV-2 INFECTION IN CANCER PATIENTS

Numerous studies have shown that COVID-19 with ‘pre-existing conditions’ especially cancer, have higher mortality rates than “healthy” population (16-fold higher risk) (FDA’s Oncology Center of Excellence).^{3,8,36,37} The estimated 19 million new cancer cases (led by breast, lung, colorectal, prostate cancer, skin and stomach cancers), 10 million deaths in 2020 (GLOBOCAN), along with the increased infection risk, make it crucial to understand the immunological interplay between cancer and SARS-CoV-2 infection. Moreover, major signaling pathways impaired by SARS-CoV-2 infection are also upregulated in patients with cancer and COVID-19,

COVID-19 and its impact on development of immunity against SARS-CoV-2 infection

5 Dysregulated immune responses in COVID-19

5.1 Dysregulated innate immune response

Normal innate immune response is essential for clearing the SARS-CoV-2 infection and for initiation of an adaptive immune response.



5.2 Dysregulated adaptive immune response

a Dysregulated T-cell response:

Normal T-cell response is essential for adaptive immunity, B-cell maturation and heterologous cross-reactive protection against SARS-CoV-2.



b Dysregulated B-cell response:

Normal B-cell response is essential for innate immunity and antibody production against SARS-CoV-2.



c Dysregulated antibody response:

Normal robust antibody response is required for protection against SARS-CoV-2.

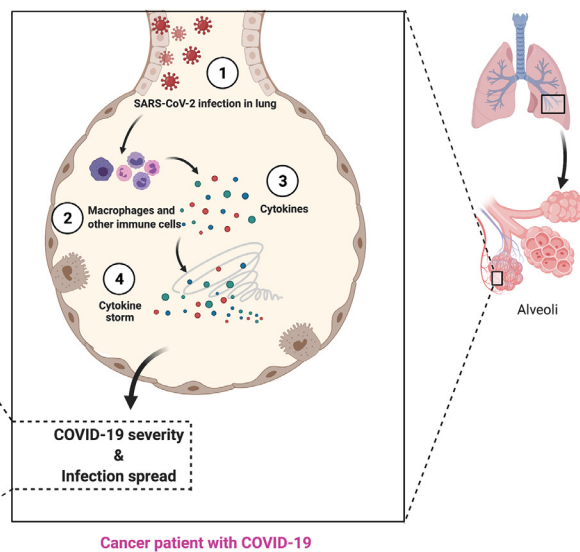


Fig 1. COVID-19 and its impact on development of immunity against SARS-CoV-2 infection. SARS-CoV-2 infect lung epithelial cells (1) and is sensed by macrophages and other innate immune cells (2). Upon sensing the SARS-CoV-2 infection, innate immune cells express cytokines (3) which accelerate the production of more cytokines and lead to cytokine storm (4). The resulting cytokine storm lead to dysregulation of immune functions and/or responses (5): dysregulated innate immune response (5.1), dysregulated adaptive immune response (5.2) – dysregulated T-cell response (a), dysregulated B-cell response (b), and dysregulated antibody response (c).

and include: cytokine signaling, type-I interferon signaling, androgen receptor signaling, and immune checkpoint signaling (Fig 2).³⁸ Untangling the complex relationships between the immune responses triggered by the many cancer types and SARS-CoV-2 infection has been an on-going challenge for the field, and will be further discussed in the following sections.

Viral infections and the associated chronic inflammatory responses have often been associated with cancer presentation and/or progression.^{37,39,40} Among viruses, a group of viruses is associated with the incidence and/or progression of cancers and are known as oncogenic viruses, for example; HIV, HPV, HBV, HCV, EBV.^{37,41-43} The designation of SARS-CoV-2 as an “oncogenic virus” and its role in tumorigenesis remain subjects of ongoing research.^{37,44} Studies looking into the link between SARS-CoV-1 infection (a virus that shares 79.6% homology at genome level with SARS-CoV-2) and cancer have reported that this virus can interfere with signaling pathways, such as p53, EGFR, JAK/STAT, or MAPK signaling, that will promote carcinogenic transformation of cells.⁴⁷⁻⁴⁹ Moreover, pro-inflammatory cytokine production during SARS-CoV-2 infection (including IL-6: a typical feature of oncogenic viruses) could drive pro-

tumorigenic activity.⁴⁴⁻⁴⁶ Even if SARS-CoV-2 does not play a direct role in cancer etiology, it still has the potential to alter the immune landscape and which would enhance adverse outcomes in patients with cancer.^{8,50,51} To understand the role of SARS-CoV-2 infection in tumor progression it is important to consider etiological differences among cancers that complicate the cancer immune landscape and drive adverse outcomes in SARS-CoV-2 infected cancer patients.

Recent epidemiological studies have reported that patients with hematological, lung or breast cancers are more likely to develop adverse outcomes that culminate in increasing the risk of hospitalization and deaths, during SARS-CoV-2 infection.^{36,52,53} Interestingly, these reported cancer types have very diverse immunopathology and hence are likely to mount distinct changes in the immune landscape during infection.⁵⁴⁻⁵⁶ Hematological malignancies and/or blood cancer are liquid (leukemias) or are localized to sites of development and/or primary ie, bone marrow or secondary lymphoid organs, unlike most solid tumors.⁵⁷⁻⁵⁹ These features make hematological malignancies highly available to interactions with immune cells and respond avidly to on-going systemic inflammatory responses (such as those observed during severe

Changes in cancer cell signaling pathways upon SARS-CoV-2 infection

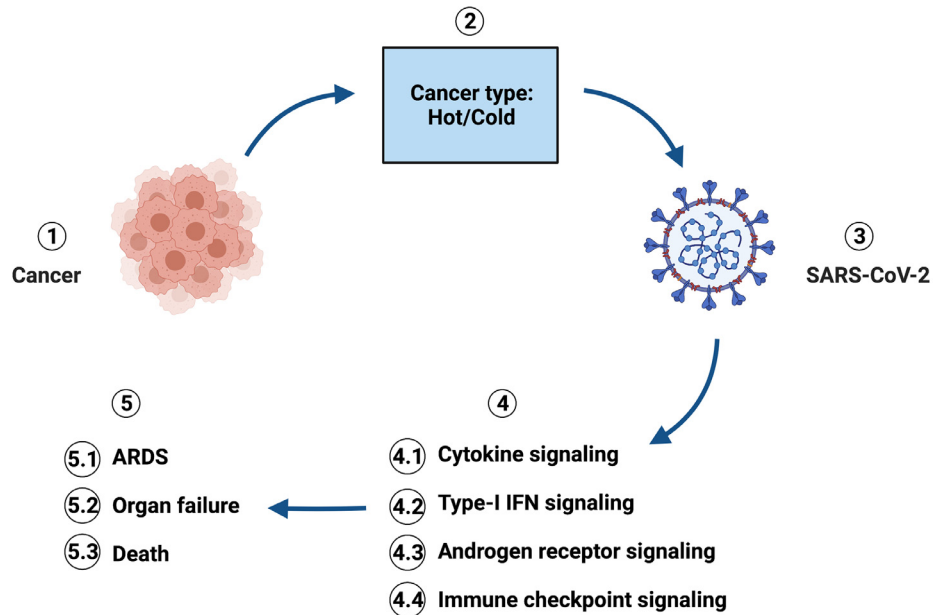


Fig 2. Changes in cancer cell signaling pathways upon Sars2 infection. Cancer (1) is heterogenous depending on the tumor micro environment: hot or cold (2), and the susceptibility of patients with cancer to SARS-CoV-2 infections (3) is influenced by cancer type. Four major signaling pathways that are common and impaired in both diseases are: cytokine, type-I IFN, androgen receptor, and immune checkpoint signaling pathways (4). These impairments in signaling pathways lead to cytokine storm that consequently ends up on acute respiratory distress syndrome (ARDS), organ failure, and death (5).

COVID-19). In this scenario, it is likely that pre-infection cancers associated inflammation synergizes with systemic immune responses seen during SARS-CoV-2 infection – resulting in a higher than usual inflammation and potentially higher mortality rates.

In contrast to hematological malignancies, lung and breast cancers are solid tumors that respectively fall under “hot” and “cold” tumor categories, respectively.^{12,60-63} Similar to most hematological malignancies, a hot tumor (like melanoma, non-small cell lung cancer, and cancers of the liver, kidney, bladder, and head and neck) shows a high level of interfacing capacity with the immune system.^{63,64} Indeed, the tumor microenvironment (TME) of hot tumors includes several subsets of innate as well as adaptive immune cells that are endowed with a wide array of effector functions.^{63,65} Specifically, cytokines and chemokines (including but not limited to; CCL2, CCL3, CCL4, CCL5, CXCL9, CXCL10, CCL17/22) produced by these tumors allow for the migration of tumor specific T cells in the TME; these T cells are responsive to immune check point blocker therapies that rescue anti-tumor T cell effector function.^{12,63-67} In contrast, cold tumors (like ovarian, breast and pancreatic cancers) are characterized as “non-inflamed” or “immune-deserts” and present with a microenvironment that presents

striking features of T-cell r exclusion from the TME.^{12,63-65,68-70} In the context of SARS-CoV-2 infection, it can be speculated that hot tumors (like lung cancer) that are immunologically active and anatomically primed will fuel the systemic inflammatory responses observed during SARS-CoV-2 infection (Fig 3). However, the exact mechanisms driving adverse outcomes with each cancer (with or without therapy) are yet to be elucidated.

IMMUNE MECHANISMS THAT DETERMINE THE ADVERSE OUTCOMES OF COVID-19 IN HOT AND COLD TUMORS

To understand the impact of these heterogenous cancer etiologies on COVID-19 outcomes, it is important to first elucidate their impact on SARS-CoV-2 entry and/or infection and existing or resulting immune cascades. Expression of ACE2 (the viral entry receptor) in lung epithelial was shown to be higher in older subjects, smokers and/or subjects suffering from smoking related disorders like chronic obstructive pulmonary disease (COPD).^{3,13,71-73} Moreover, expression of TMPRSS2, a membrane-bound serine protease known to synergize with ACE2 to promote SARS-CoV-2

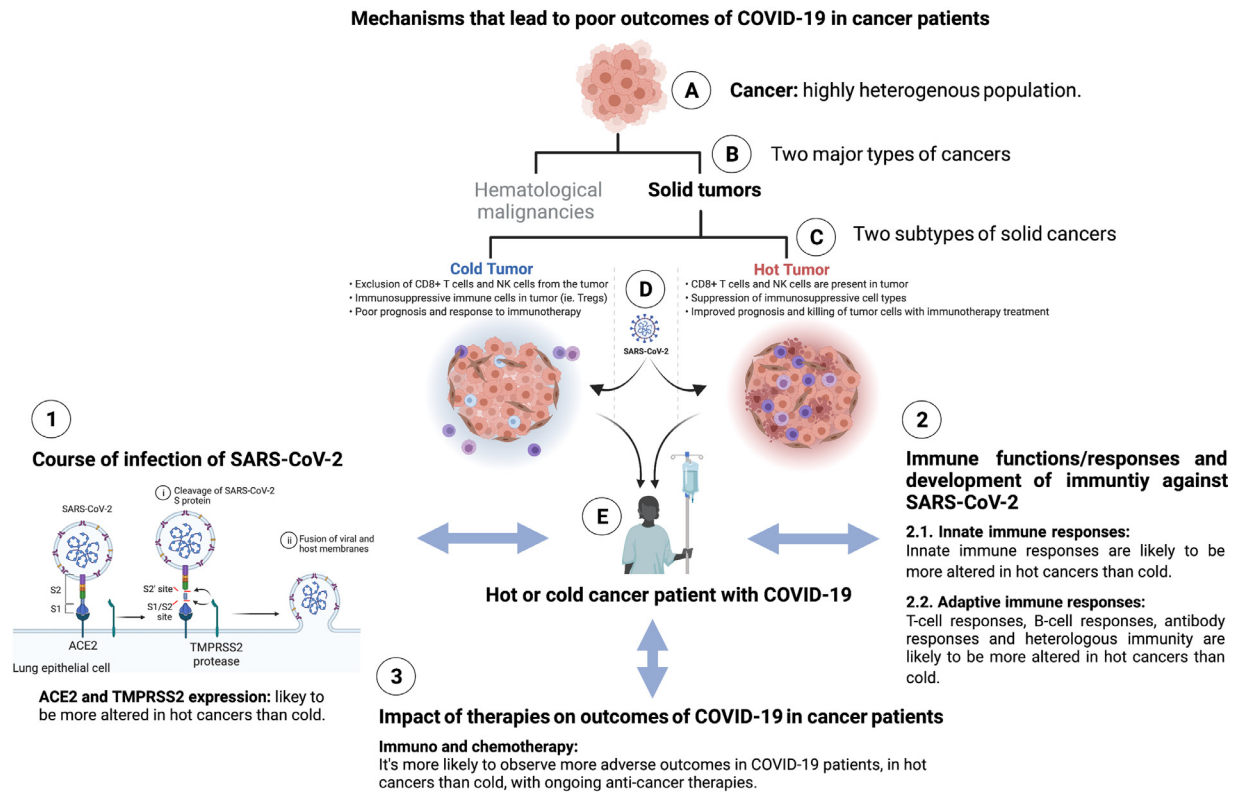


Fig 3. Mechanisms that lead to poor outcomes of COVID-19 in cancer patients. Cancer patients are highly heterogeneous population (A) and are divided into two major categories; hematological malignancies and solid tumors (B). Solid tumors can be further divided into hot tumor and cold tumor groups (C), which can get infected by SARS-CoV-2 (D) and develop COVID-19 (E). Course of infection of SARS-CoV-2 (1) – influenced by differential expression of ACE2 and TMPRSS2 in hot vs cold cancers – can lead to poor outcome of COVID-19 in hot vs cold cancer patients. Immune responses and development of immunity against SARS-CoV-2 (2) – influenced by differential innate (2.1) as well as adaptive (2.2) immune responses in hot vs cold cancers – can lead to poor outcome of COVID-19 in hot vs cold cancer patients. Impact of therapies (3) – influenced by immunotherapy as well as chemotherapy in hot vs cold cancers – can lead to poor outcomes of COVID-19 in hot vs cold cancer patients.

entry, has also been observed to be highly expressed in prostate cancer (cold cancer), where it is upregulated by androgen receptor (AR).⁷⁴⁻⁷⁶ Interestingly, in two recent studies, prostate cancer (cold cancer) patients not treated with androgen deprivation therapy (ADT) were more likely to be infected by SARS-CoV-2, suggesting a possible relation of the increased expression of TMPRSS2 and the development of severe COVID-19 in patients with cold tumors like prostate cancer.^{17,77} Based on these data, it can be hypothesized that the increased expression of ACE2 and TMPRSS2, mainly due to pro-inflammatory conditions, in subjects with factors known to be associated with lung cancer incidence could lead to increased viral titers and development of severe COVID-19 (Fig 3).

Innate immune responses and development of severe SARS-CoV-2 in hot vs cold cancer. The innate immune response is the first line of defense against SARS-CoV-2 infection.⁷⁸⁻⁸⁰ SARS-CoV-2 infection is sensed by

pathogen recognition receptors (PRRs) – mainly by RIG-I Like Receptors (RLRs); MDA5 and LGP2, and NOD Like Receptors (NLRs); NOD1 – in the lung epithelial cells, and innate immune response is initiated.^{79,80} Upon induction of innate immune response, cells in lung epithelium – epithelial cells as well as immune cells – produce proinflammatory cytokines, chemokines, interferons (IFNs); type-I and type-III, and IFN stimulated genes (ISGs).⁸⁰⁻⁸⁴ However, type-I and type-III IFN defined innate immune response in COVID-19 are dysregulated and its kinetics set the severity and future pathological outcomes of the disease.^{83,85,86} For example, the initial type-I and type-III IFNs response is higher in patients with mild and/or moderate COVID-19 while it is reduced in severe COVID-19 patients.^{83,85,86} In particular, COVID-19 patients in critical condition (severe COVID-19) exhibit increased frequencies of innate immune cells – mainly neutrophils, monocytes and

macrophages – that produce increased level of cytokines which results in the cytokine storm. Cytokine storm induction is correlated with the severity of COVID-19 and its adverse outcomes.^{84,86,87}

At present, very limited knowledge is available on SARS-CoV-2 specific innate immune responses in patients with cancers. Compromised innate immune response in patients with cancers make cancer patients more susceptible to SARS-CoV-2 infection.^{8,88-90} Higher frequencies of adverse outcomes of COVID-19 inflicted by the dysregulated innate immune responses are likely in patients with hot cancers than the patients with cold cancers, because of increased immune compromised environment of hot cancers than the cold cancers (Fig 3).⁹¹ Specifically, lung cancer (a hot cancer) has active but compromised and/or exhausted lung TME and thus has a disrupted innate immune response against SARS-CoV-2 infection.^{91,92} The immune activation profile of TME in lung cancer – infiltrated with immune cells and chronically inflamed – can fuel up the dysregulation of innate immune responses against SARS-CoV-2 in lungs.^{10,91} Moreover, cytokine storm could occur in tumor cells too, because of several underlying factors, and that can impact the innate immune responses mounted against SARS-CoV-2 infection as well as the severity of COVID-19.⁹² On the other hand, dysregulation of innate immune response in consequence of SARS-CoV-2 infection can facilitate the growth of lung cancer and/or other tumors.⁹¹

Adaptive immune responses and the development of severe SARS-CoV-2 in hot vs cold cancer. At present, very few studies have focused on deciphering SARS-CoV-2 specific adaptive immune responses in patients with cancers. In SARS-CoV-2 infection, classic antiviral responses – where anti-viral cytotoxic CD8 T-cell responses (aided by a CD4 T-cell driven T-helper 1 response) limit viral persistence by killing virus infected host cells – are disrupted and a rapid depletion of CD4 T-cells, CD8 T-cells and B-cells is observed (Fig 3).⁸⁷ Recently, Mansi et al. showed that although cancer patients failed to mount T-cell responses against SARS-CoV-2, no impact on the pre-established immune memory against common viruses in SARS-CoV-2 infected patients was observed, arguing that the impaired SARS-CoV-2 specific T-cell responses can be used as a determinant for adverse outcome of COVID-19 in cancer patients.⁹³

As discussed above, the outcome of SARS-CoV-2 infection can be shaped by the immune microenvironment of a tumor. On the one hand, while hot TME is highly dynamic and allows for immune cell infiltration, cold tumors lack immune cell infiltration, suggesting that the impairment of pre-existing anti-tumor T-cells responses in cancer patients that acquire SARS-CoV-2 infection would

be greater in hot cancers or hematological cancers that regularly interface with immune cells. In addition to pre-existing anti-tumor T-cells, heterologous immunity – a phenomenon of protection in which an individual develops pathogen-specific T-cells against an unencountered pathogen after being exposed to cross-reactive non-identical pathogens⁹⁴⁻⁹⁸ – is also observed in SARS-CoV-2 unexposed individuals.^{97,99-101} This is particularly true in individuals that have higher frequencies of T cells with responses to cross-reactive epitopes shared by common human coronaviruses (HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1).^{101,102} Because of increased T-cell activity in hot or HM tumors, impairments in cross-reactive immunity may be expected. A recent study by Bilich et. al. showed reduced prevalence of pre-existing cross-reactive CD4 T-cell responses against SARS-CoV-2 in unexposed patients with HMs compared to patients with solid tumors.⁹⁷ Moreover, the unexposed subjects with HMs presented signs of T-cell exhaustion (higher proportion of T cells expressing PD-1, LAG3, and TIM3) and reduced magnitude, diversity, and persistence (memory) of SARS-CoV-2 specific T-cell immunity.⁹⁷ In addition to T-cells, B lymphocytes (B-cells) also play a critical role in protecting against SARS-CoV-2 infection by producing neutralizing anti-viral antibodies. Although B cells have not been extensively studied in cancer patients with COVID-19, Mansi et al. have shown that SARS-CoV-2 patients with solid tumors or HMs produced high titers of virus specific antibodies, which could compensate for an impaired T cell response.⁹³

Impaired T and B-cell responses can result from damage to specific organs, like the lymph nodes (LNs).¹⁰³⁻¹⁰⁵ Indeed, SARS-CoV-2 infection causes swelling and inflammation of lymph nodes, which can progress to LN fibrosis, prevent germinal center formation of and consequently disrupt healthy virus specific T-cell responses and neutralizing antibody production.^{18,19,106} Lymph nodes of COVID-19 patients with lung carcinoma metastatic cancer – a cancer known to have compromised innate (such as, IFN-I and IFN-III) and T-cell (memory T_H1) responses in mediastinal lymph nodes – were found to be enlarged with tissue structure disruption and immune cell dysregulation, including macrophage accumulation and lymphopenia.^{18,19,106} Although little is known about lymphedema in SARS-CoV-2 infected cancer patients, it can be postulated that like in HIV infection, increased concentrations of lymphatic TGF- β and IL-1 β might play a major role in the development of LN fibrosis^{107,108} which would impact on adaptive immune responses. Further studies to clarify the decipher the impact of these LN fibrosis inducing cytokines on priming adaptive cellular and humoral responses to SARS-CoV-2 infection need to be conducted.

IMPACT OF CANCER THERAPIES ON COVID-19 OUTCOMES IN HOT VS COLD CANCER

Anti-cancer therapies. Stratifying groups of cancer patients based on the type of treatment, stage of treatment, dosage of treatment etc. could provide better insights into the outcomes of COVID-19 in infected patients. Studies have shown that the immune system of patients with cancer undergoes diverse alterations due to the various treatment regimens they receive.^{3,45} Traditional anti-cancer therapies like chemotherapy cause bone marrow suppression which leads to thrombocytopenia and neutropenia, while DNA damage to lymphocytes caused by radiation therapy can cause lymphopenia.^{3,13,45,109,110} The depletion of leukocytes in conjunction with the use of corticosteroids and other immunosuppressive therapeutics impair immune responses against even the most common bacterial and viral pathogens and this compromised immunity could contribute to increased incidence of COVID-19 related adverse outcomes in cancer patients (Fig 3).^{13,45,110} Epidemiological studies have reported mixed results on the association between chemotherapies and COVID-19 associated adverse outcomes. In a Japanese seroprevalence study, Ab levels against SARS-CoV-2 nucleocapsid (but not spike) protein were lower in cancer patients who received chemotherapy treatment within 1 month compared with those who did not receive it.¹¹¹ A study from Israel also reported that IgG levels were significantly lower in patients who received combined chemotherapy with immunotherapy (commonly administered in specific cancers like lung cancer (hot cancer), triple-negative breast cancer (cold cancer)).^{112,113} Unlike chemotherapy, immunotherapies (immune check inhibitors, adoptive cell therapies, cancer vaccines etc.) that help prime the immune system to kill cancer cells, could be advantageous in this scenario and could help in mounting anti-SARS-CoV-2 responses.¹¹⁴

Cancer is often characterized by a state of systemic chronic inflammation. However, several tumors require interventions that rejuvenate immune responses within the host TME. These therapies include the use of immune checkpoint inhibitors (ICIs), cytokine-based therapies, chimeric antigen receptor T (CAR-T) cell therapy, bispecific T cell engagers (BiTEs), and allogeneic stem cell transplantation.^{3,45,115-117} Although these therapies drive efficacious anti-tumor responses they also induce systemic inflammation and the cytokine storm that can harm normal healthy tissues (eg, pneumonitis) and predispose the patient to adverse effects that are associated with SARS-CoV-2 infection.^{3,45,118,119} Most commonly, the use of immunotherapies, such as CAR-T and CTLA-4 therapies,

can promote systemic immune hyperactivation that results in the clinical manifestation of cytokine release syndrome.^{45,115,118,120} Indeed, it has been observed that cytokines that mediate efficacious ICI responses during CAR-T cell and BiTE therapy (IFN- γ , TNF- α , IL-2 and GM-CSF) are also some of the prime conductors of cytokine storm.^{3,121-123} However, a recent report showed that the prior anti-PD-1 therapy – an ICI that is widely used to treat lung cancer – does not appear to impact the severity of COVID-19 in patients with lung cancers. That is contrary to the assumptions that the prior use of ICIs in cancer patients can dampen the inflammation and severity of COVID-19 disease.⁵² Clinical studies aimed at elucidating the impact of immunotherapies on the manifestation of adverse outcomes in COVID-19 patients have showed conflicting results.^{6,124,125}

Vaccine and alternate therapies for efficacious response to SARS-CoV-2 infection in cancer patients. Impairments of B-cell responses contribute to proper but delayed COVID-19 vaccine responses in patients with cancers. However, the extent to which cancer heterogeneity contributes to this impairment remains unclear. COVID-19 vaccine recipients with solid tumors were observed to have humoral immune responses; anti-SARS-CoV-2 spike (S) IgG, comparable to those observed in healthy subjects; of note low cellular responses were monitored in these patients.¹²⁶ Whereas patients with HMs elicited suboptimal humoral and cellular immune responses.¹²⁶ In addition, antibody titers sharply decreased within 3 months of vaccination for most of cancer patients (most prominently for patients with HMs).¹²⁶ In another controlled mRNA vaccine immunization study, Shroff et al., 2021, it was found that neutralizing antibodies were produced in 67% and 80% of cancer patients after the primary and secondary vaccine shots, respectively¹²⁷ as compared to healthy controls. A further 3-fold increase in median titers was observed upon booster immunization.¹²⁷ Quantification of antigen (RBD and Spike S1) specific memory B-cell subsets, revealed that frequencies of spike-specific memory B-cells required two immunizations in cancer patients vs a single immunization in healthy subjects¹²⁷ further indicating that a third vaccine dose might help enhance antibody responses in patients with cancers. This lower or non-responsiveness to COVID-19 vaccine by cancer patients is further confirmed in a recent study from US which reported that 46% of the patients with HMs – 31 out of 67 patients – did not produce detectable anti-SARS-CoV-2 spike antibodies following two shots of the Pfizer-BioNTech COVID-19 vaccine. These 31 patients were considered “non-responders” to the COVID-19 vaccine.¹²⁸ Another study showed that the seroconversion

– the time from vaccination to the availability of virus specific antibodies in the blood – rate for COVID-19 was only 55% in cancer patients following one dose of Pfizer-BioNTech, though it reached 100% in the control group (25 subjects).¹²⁹ That being said, these promising observations have been confounded by reports that some cancer patients fail to respond to the SARS-CoV-2 vaccine at all (Fig 4). These poor vaccine specific antibody responses could result from sub-optimal T/B-cell priming and collaboration that is a consequence of the fibrosis (driven by excessive TGF-β) which disrupts the LN architecture. Further studies to understand the mechanisms that underlie poor immune response to vaccine in SARS-CoV-2 infected cancer patients are still needed.

Given the poor COVID-19 vaccine efficacy in cancer patients, it becomes increasingly important to find alternate means of treating SARS-CoV-2 infected cancer patients (Fig 4). Alternate treatments that modulate the immune system by reducing aberrant inflammation and

improve T-cell function (cytokine blockers and ICIs) could benefit this population.¹³⁰⁻¹³² Two primary systemic innate immune cytokines that mediate the pathology of cytokine release syndrome are IL-1 and IL-6.^{133,134} IL-1, the master orchestrator of inflammatory responses in COVID-19, promotes innate immune activation and drives the production of proinflammatory molecules.¹³³ IL-1 inhibitors, approved by the Food and Drug Administration (FDA) – already available in the market – either bind directly to IL-1 (Rilonacept and Canakinumab) or block IL-1 binding to the IL-1 receptor (Anakinra).^{130,135} Like IL-1, elevated IL-6 levels in patients with severe COVID-19 identifies can also be targeted by existing FDA approved agents that either directly target IL-6 (Clazakizumab, Siltuximab, Sirukumab and Olokizumab), IL-6 cognate receptor (Sarilumab and Tocilizumab) or block IL-6 trans-signaling (Olamkicept) by blocking the soluble IL-6 receptor (sIL-6R).¹³⁴ Although preliminary studies have yielded conflicting results in patients with mild to moderate COVID-19, the use of IL-6 in patients with

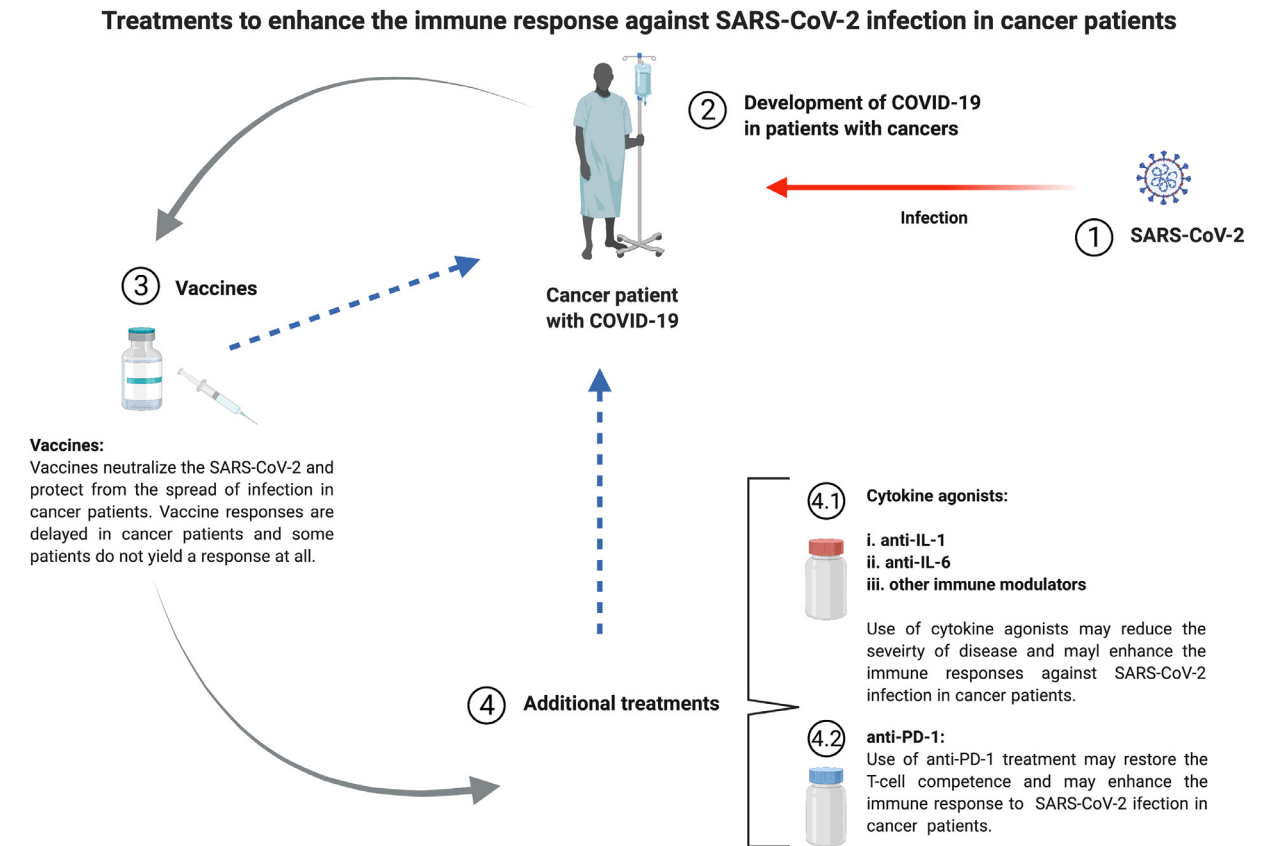


Fig 4. Treatments to enhance the immune response against SARS-CoV-2 infection in cancer patients. SARS-CoV-2 infect individuals with cancers (1) and SARS-CoV-2 infected individuals develop COVID-19 (2). COVID-19 vaccine is the first strategy to protect immunocompromised individuals, particularly cancer patients, from SARS-CoV-2 infection (3). Additional treatments are required for the cancer patients who cannot acquire protection, against COVID-19, through vaccine (4). Additional treatments include cytokine agonists (4.1): anti-IL-1 (a), anti-IL-6 (b), other immune modulators (c), and anti-PD-1 (4.2).

severe COVID-19 is still seen as a viable treatment option.^{136,137} Other compounds that may have therapeutic potential in severe COVID-19 include inhibitors against: interferons (α , β , γ), kinases (JAK, MAPK, PI3K), GM-CSF, CCR, NF- κ B and JAK/STATs.¹³⁸ In fact, the JAK inhibitor “baricitinib” has been approved by FDA for emergency use in combination with “remdesivir” (FDA).¹³⁹ Further investigation into mechanisms that drive these pro-inflammatory responses must be conducted in order to identify therapeutics for cancer patients with severe COVID-19 infections.

Another promising option to treat the COVID-19 patients with cancers is the use of PD-1 inhibitors (Fig 4). While PD-1 blockade has improved the survival rate of patients with multiple incurable cancers, the potential beneficial therapeutic impact of PD-1 blockade is unknown in context of COVID-19 patients with cancers.¹⁴⁰ Like cancer patients, increased frequencies of PD-1 expressing T-cells are observed in COVID-19 patients.¹⁴¹ It can be argued that, although on the one end therapies like PD-1/PD-L1 blockade (that restore T-cell competence in cancer and chronic viral infections) may enhance detrimental hyperimmune response in COVID-19 patients, they could provide much needed immunological control of viral infections.¹⁴² Current clinical trials aimed at evaluating the efficacy of anti-PD-1 antibody administration to both cancer and non-cancer patients with COVID-19 are underway, and may help in understanding whether restoring the competence of PD-1 expressing T-cells can efficaciously control SARS-CoV-2 infection.¹⁴⁰

RELEVANCE TO CANCER CARE

The impact of COVID-19 pandemic on cancer patients is far reaching. Early in the pandemic, there was a great need to divert health care resources to address a rapidly growing numbers of COVID-19 patients, as well as to protect healthy individuals from SARS-CoV-2 infection by suspending non-urgent health care (American Cancer Society). Clinical trials for finding new cures have also been affected by the COVID-19 pandemic, with 60% of research programs suspending screening and/or enrollment of subjects for clinical trials.¹⁴³ A large portion of research funds have been invested in COVID-19 clinical trials; more than 6442 ongoing studies are listed in clinicaltrials.gov, as of September 2021. While these measures were essential, delays in cancer screening, diagnosis, and treatment due to the restricted access to care will most likely result in missed diagnoses and an increase in late-stage diagnoses and preventable cancer deaths.¹⁴³⁻¹⁴⁸ The adverse impact of the pandemic on

cancer care can be expected to translate into increased cancer mortality over the coming years.

PERSPECTIVES

Caveats of these studies include, but are not limited to: (1) short duration studies, (2) the small sample size for cancer patients with COVID-19, (3) the very heterogeneous profile of the cancer patient cohorts in terms of cancer type, status of the cancer, nature of treatment, status of treatment, (4) lack focus on defining the mechanisms involved in adverse outcomes for cancer patients with COVID-19. Given the complexity and heterogeneity of the cancer population in context of SARS-CoV-2 infection, an unbiased systems biology approach would be very useful to understand mechanisms and identify therapeutic targets that can aid in improving outcomes in SARS-CoV-2 infected cancer patients.

FINAL SUMMARY

The impact of the ongoing COVID-19 pandemic is being felt in subjects that have a pre-disposed immunocompromised profile (eg, cancer patients). Due to the immense heterogeneity (type and treatment of tumors) among the cancer populations, conflicting observations of adverse outcomes to SARS-CoV-2 infection have been reported. Mechanistic understanding of how infections progress in homogenous cancer populations will help develop therapeutics that can restrain adverse outcomes and promote healthy recovery.

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