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At the Crossroads: COVID-19 and Immune-Checkpoint Blockade for Cancer

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Abstract

The immunomodulatory effects of immune-checkpoint blockade (ICB) therapy for cancer may act at the crossroads between the need to increase antiviral immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and to decrease the inflammatory responses in severe cases of coronavirus disease 2019 (COVID-19). There is evidence from preclinical models that blocking programmed death receptor 1 (PD1) protects against RNA virus infections, which suggests that patients with cancer receiving ICB may have lower rates of viral infection. However, given the heterogeneity of patient characteristics, this would be difficult to demonstrate using population-based registries or in clinical trials. Most studies of the impact of ICB therapy on the course of COVID-19 have centered on studying its potential detrimental impact on the course of the COVID-19 infection, in particular on the development of the most severe inflammatory complications. This is a logical concern as it is becoming clear that complications of COVID-19 such as severe respiratory distress syndrome are related to interferon signaling, which is the pathway that leads to expression of the PD1 ligand PD-L1. Therefore, PD1/PD-L1 ICB could potentially increase inflammatory processes, worsening the disease course for patients. However, review of the current evidence does not support the notion that ICB therapy worsens complications from COVID-19, and we conclude that it supports the continued use of ICB therapy during the COVID-19 pandemic provided that we now collect data on the effects of such therapy on COVID-19 vaccination.

Introduction

Antibodies blocking immune checkpoints are used to treat patients with multiple cancer histologies, and this type of treatment has the potential to affect the course of other human diseases. Of key timely importance is understanding the effects of such treatment, which is referred to as immune-checkpoint blockade (ICB) therapy, on coronavirus disease 2019 (COVID-19). There are potential beneficial and detrimental consequences to receiving ICB therapy during the COVID-19 pandemic (Fig. 1). The available data are continually

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evolving, and there is a need to keep monitoring the clinical situation as we move to a new phase of the pandemic during which patients with cancer who are being treated with ICB will be receiving COVID-19 vaccinations (1).

How Could ICB Therapy Be Beneficial or Detrimental during COVID-19?

ICB therapy could potentially have a beneficial effect during COVID-19 by decreasing the rate of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or by preventing the virus from replicating upon infection. This is because releasing immune checkpoints can increase T-cell responses to both cancer and viruses. One of the first conclusive demonstrations of the ability of programmed death 1 (PD1) blockade to induce a therapeutic immune response was in an RNA virus mouse model where anti–PD-1 therapy reinvigorated exhausted antiviral T-cell responses (2). Furthermore, there is good evidence that T cell–mediated immune responses to viruses can protect against infection, including T-cell responses to SARS-CoV-2 in humans (3, 4). In addition, T cells from patients infected with RNA viruses like dengue virus and SARS-CoV-2 frequently express PD1, in particular virus-specific T cells (4–6). Finally, clinical evidence that ICB therapy targeting cytotoxic T lymphocyte antigen 4 (CTLA4) or PD1 decreases RNA viremia comes from patients with chronic viral hepatitis receiving ICB for the treatment of hepatocellular carcinoma (7, 8).

It is difficult to conclusively determine if ICB therapy protects against COVID-19, and it is likely a question that may not be answered soon. Population-based registries reporting on the incidence of COVID-19 in patients with cancer receiving ICB therapy compared with patients with cancer not receiving ICB or individuals without cancer are likely to be plagued by multiple confounding factors. Such analyses will not provide conclusive evidence of decreased rates of infection or a more benign course of COVID-19 in patients who otherwise would have similar exposures and risk factors for COVID-19 infection. Conclusive evidence that ICB therapy decreases the frequency of SARS-CoV-2 infection would require conducting very large randomized trials in which healthy subjects would receive ICB therapy or placebo in a manner similar to the conduct of the current COVID-19 vaccine trials. Such trials would not be justified due to the frequency of immune-related adverse effects of ICB therapy, which would be unacceptable as a therapy to prevent virus infection. Another way to test if ICB therapy has a beneficial effect on COVID-19 in humans would be to select a population of patients with cancer who are receiving ICB and then perform a planned exposure to SARS-CoV-2. Such a study would likely be deemed to be not ethical given the higher risk of COVID-19 complications in patients with cancer and other comorbid conditions (9, 10). Therefore, despite the experimental and scientific rationale, we may not learn if ICB therapy results in protection against SARS-CoV-2 infection or improvement of the course of COVID-19.

The specific mechanisms that lead to the inflammatory changes resulting in severe complications of COVID-19 are still not clear. Nor are the mechanisms by which ICB therapy may worsen or improve these pathologic processes. Relevant to these questions is the observation that SARS-CoV-2 has developed a series of mechanisms to downregulate type I and type III interferon responses, which are the main initial processes during an innate immune response, paving the way to an adaptive and long-term protective immune response

(6, 11). Despite low levels of type I and type III interferons, there is evidence that IFNγ, a type II interferon, is induced during SARS-CoV-2 infection (6). This may lead to expression of PD-L1 that could interact with PD1, which is frequently expressed by antiviral T cells (4). There is also evidence that interferons induce expression of ACE2, which is critical for SARS-CoV-2 to infect human cells (12). These data indicate that it is likely that PD1–PD-L1 interactions exist in individuals infected with SARS-CoV-2, suggesting that the use of PD1 blockade therapies has the potential to worsen the course of COVID-19. On the other hand, given the key role of interferons in protecting against COVID-19 (13) and their lower levels in severe cases of COVID-19, it is possible that high levels of IL6 and TNFα (6) may be the key cytokines inducing proinflammatory changes away from the induction of an adaptive immune response mediated by IFNγ. If this is the case, then PD1 blockade therapies might be expected to improve antiviral responses without increasing the deleterious inflammatory processes leading to severe complications from COVID-19.

What Is the Clinical Evidence for a Beneficial or Detrimental Effect of ICB Therapy in COVID-19?

Elucidating if the potential effects of ICB on SARS-CoV-2 infection and the course of COVID-19 are evident in humans requires careful analysis of clinical data. At the beginning of the pandemic, there was an initial widespread tendency to discontinue cancer treatments as it was unknown if they could affect the severity of COVID-19 and also to reduce the number of people in hospitals. Among the frequently paused or discontinued treatments was ICB therapy. However, suspending or reducing treatments indefinitely could result in an increase in overall cancer mortality given the demonstrated improvement in patient outcomes when using cancer immunotherapies. For this reason, there have been a large number of publications, case reports, case series, and registries seeking to shed light on the outcomes of patients with cancer who became infected with SARS-CoV-2. For this perspective, we reviewed these series and focused on data that provide enough information to avoid the conclusions being driven by associated conditions and confounding factors (Table 1).

The COVID-19 and Cancer Consortium (CCC-19) is a global registry collecting reports on adult individuals with a current or historical invasive solid or hematologic malignancy who have been diagnosed with COVID-19, with or without laboratory confirmation of SARS-CoV-2 infection. Analysis of 3,899 persons showed that the presence of a progressive cancer, recently having received a cancer therapy, hematologic malignancies, and the coexistence of multiple malignancies were all factors associated with an increased risk of 30-day mortality (14). Additional analyses on the correlation between timing of anticancer treatment and COVID-19–related complications demonstrated that mortality was higher in patients with any active cancer compared with those in a complete remission (14). There was an increased risk for patients on chemoimmunotherapy, targeted therapies (mainly antiangiogenics), and anti-CD20 therapy, but there was no evidence of worse outcomes for patients on ICB therapy alone. However, numbers of patients on chemoimmunotherapy were very small, rendering the interpretation of results still debatable. The UK Coronavirus Cancer Monitoring Project (UKCCMP) is a prospective observational study that enrolled

patients with cancer presenting to their network of cancer centers (15). UKCCMP reported results on 800 patients with a diagnosis of cancer and symptomatic COVID-19. After adjusting for age, gender, and comorbidities, they found no significant effect on mortality for patients treated with chemotherapy, immunotherapy, hormonal therapy, targeted therapy, or radiotherapy within the past four weeks when compared with patients with cancer who had not recently received such therapies. The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry is a multicenter observational study composed of a cross-sectional component and a longitudinal cohort component (16, 17). Eligibility criteria were the presence of any thoracic cancer and a COVID-19 diagnosis. Analysis of 1,052 patients suggested that chemotherapy, but not immunotherapy, was associated with an increased risk of death (18). Another observational study of the natural history and outcomes of European patients with cancer during the COVID19 pandemic identified 890 patients with confirmed SARS-CoV-2 infection and cancer at the 19 centers surveyed in the United Kingdom, Italy, Spain, and Germany (19). Outcomes among the 56 patients receiving immunotherapy were no worse than for those not receiving immunotherapy. The authors demonstrated a worsening gradient of mortality from breast cancer to hematologic malignancies and showed that male gender, older age, and number of comorbidities identified subsets of patients with significantly worse mortality rates from COVID-19, but not treatments.

Tian and colleagues reported on a multicenter, retrospective, cohort study, that included patients with any type of malignant solid tumor or hematologic malignancy who were admitted to nine hospitals in Wuhan, China (20). Enrolled patients were statistically matched (2:1) on the basis of age, sex, and comorbidities with patients admitted with COVID-19 who did not have cancer. 13,077 patients with COVID-19 were admitted to the nine hospitals in Wuhan; 232 patients with cancer and 519 statistically matched patients without cancer were analyzed. Patients with cancer were more likely to have severe COVID-19 than patients without cancer, but no specific cancer treatments were associated with an increased risk of death. In contrast, among 423 cases of symptomatic COVID-19 reported by the Memorial Sloan Kettering Cancer Center, age older than 65 years and treatment with ICB therapy were predictors for hospitalization and severe disease. In this series, patients receiving chemotherapy or who had recently undergone major surgery were not at higher risk for severe COVID-19 (21). However, these results were not well controlled for covariates, as reanalysis of the subset of 102 patients with lung cancer demonstrated that cancer-specific features, including prior thoracic surgery, radiation, and recent systemic therapies including ICB therapy, did not affect the severity of COVID-19 (22, 23). Conversely, patient-specific features, including smoking status and chronic obstructive pulmonary disease, were associated with worse outcomes with COVID-19. Of note, these are features that predict a higher frequency of use of ICB therapy in patients with lung cancer, thereby being confounding factors when analyzing the association of ICB therapy with COVID-19 outcomes. Finally, another series reporting on case fatality rates in 218 patients with cancer hospitalized in New York concluded that patients receiving immunotherapy did not show any associations with mortality (24).

Given the large amount of information generated in a short period of time and the lack of conclusive information, there have been several recent meta-analyses of the published

literature, which is a continuously moving target. One meta-analysis reporting on a total of 17 studies comprising 3,581 patients with cancer who also had COVID-19 concluded that patients who recently received anticancer treatment did not have a higher risk of COVID-19 exacerbation and mortality (9). However, when the authors conducted a series of subset analyses exploring different relations between timing of therapy and COVID-19 infection, chemotherapy administered within 28 days before a COVID-19 diagnosis increased the risk of death events, and ICB therapy within 90 days increased the risk of COVID-19 exacerbation. Because the overall meta-analysis suggested that ICB was not associated with increased risk of exacerbation and mortality in patients with cancer with COVID-19, these findings do not demonstrate an evident influence of immunotherapy on the development of severe COVID-19. A second meta-analysis that included 15 studies with a total of 3,019 patients with cancer and COVID-19 showed that after multivariate analysis, only age greater than 65 years and being male were associated with an increased risk of severe COVID-19 events (10). There was no evidence that immunotherapy, targeted therapies, or chemotherapy increased the fatality rate.

Conclusions

In conclusion, there is currently no evidence that ICB therapy increases the risk of death from COVID-19 in patients with cancer. We acknowledge that the registries and large retrospective cohorts have a number of biases, but they indicate that there are no noticeable increases in mortality or toxicity that can cause us to worry. Based on these results, we feel we can support continuing treatment with these agents, which have improved the prognosis of so many patients. However, we are entering a new phase of the COVID-19 pandemic, one in which patients with cancer will undergo COVID-19 vaccination. Data on those patients undergoing ICB therapy must immediately be collected because of the biological effects of ICB therapy on T-cell activation. It is imperative that we understand how this might affect the activity and safety of the COVID-19 vaccines and whether the vaccines affect safety and efficacy profile of ICB therapy.

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Authors' Disclosures

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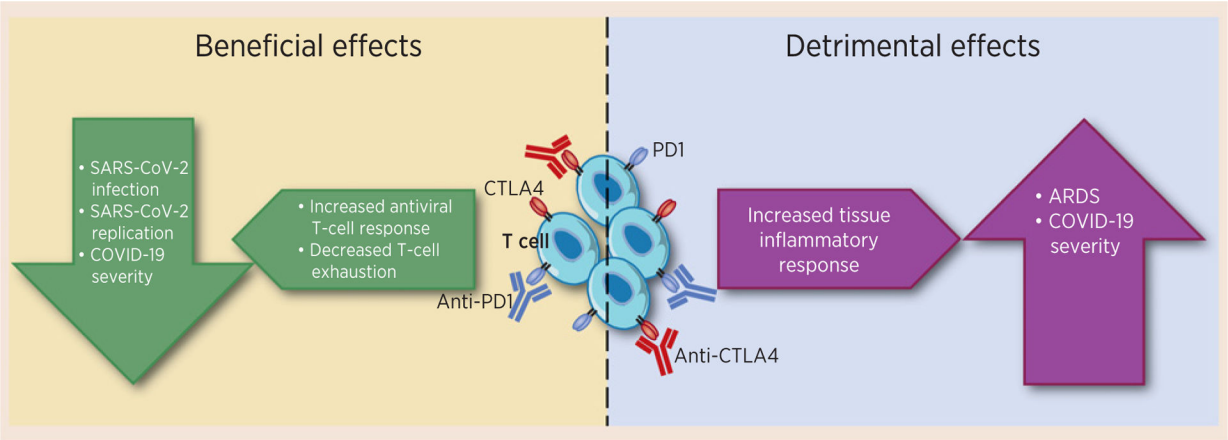

Figure 1.

ICB therapy in patients with cancer has the potential to have beneficial or detrimental effects on infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the course of coronavirus disease 2019 (COVID-19). Blocking immune-checkpoint proteins like programmed death 1 (PD1) or cytotoxic T lymphocyte antigen 4 (CTLA4) may improve antiviral responses against SARS-CoV-2, decreasing the rate of infection or mounting a stronger immune response to the virus leading to lack of viral replication and less serve COVID-19 outcomes. Conversely, blocking immune checkpoints may result in enhanced inflammatory responses to the host induced by increased interferon pathway signaling, resulting in severe complications such as acute respiratory distress syndrome (ARDS).

Table 1.

Summary of relevant registries and series reporting on ICB therapy in patients with COVID-19.

Series	Therapy	Number of patients	Readout	Effect[a]	95% CI	Reference
CCC-19						
Wise-draper et al.	Single-agent PD1 blockade[b]	62	SMR	0.92	0.44–1.69	(14)
	ICB + chemotherapy[b]	55	SMR	1.14	0.57–2.04	
	Single-agent PD1 blockade[c]	27	SMR	2.11	1.01–3.89	
	ICB + chemotherapy[c]	18	SMR	NA	NA	
UKCCMP						
Lee et al.	Single-agent PD1 blockade	17	CFR	22.7	11.5–37.8	(15)
TERAVOLT						
Garassino et al.	Single-agent PD1 blockade	132	OR	0.75	0.49–1.15	(16, 18)
	ICB + chemotherapy	147	OR	0.95	0.64–1.47	
OncoVID						
Pinato et al.	Single-agent PD1 blockade	56	OR	1.12	0.59–2.14	(19)
Tian et al.	Single-agent PD1 blockade	11	CFR	50	6.8–93.2	(20)
Robilotti et al.	Single-agent PD1 blockade	25	SMR	20%	NA	(21)
Mehta et al.	Single-agent PD1 blockade	41	OR	1.01	0.27–3.97	(24)

Abbreviations: CCC-19, COVID-19 and Cancer Consortium; CFR, case fatality ratio; CI, confidence interval; NA, not available; OR, odds ratio; SMR, standardized mortality ratio; TERAVOLT, Thoracic Cancers International COVID-19 Collaboration; UKCCMP, UK Coronavirus Cancer Monitoring Project.

[a]Ratios, case fatality rates, or percent effect.

[b]Within 2 weeks from COVID-19 diagnosis.

[c]Within 2 to 4 weeks from COVID-19 diagnosis.