Immune Checkpoint Inhibitors for Cancer Therapy in the COVID-19 Era

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ABSTRACT

The potential immune intersection between COVID-19 disease and cancer therapy raises important practical clinical questions and highlights multiple scientific gaps to be filled. Among available therapeutic approaches to be considered, immune checkpoint inhibitors (ICI) seem to require major attention as they may act at the crossroads between cancer treatment and COVID-19 disease,

due to their profound immunomodulatory activity. On the basis of available literature evidence, we suggest guidance to consider for treating physicians, and propose areas of clinical and preclinical investigation. Comprehensively, although with the necessary caution, ICI therapy seems to remain a suitable therapeutic option for patients with cancer during the COVID-19 pandemic.

Introduction

During this challenging period of the coronavirus (COVID-19) pandemic, the scientific community and patients with cancer are thoughtfully considering the possible interference of cancer treatment on the clinical course of COVID-19 infection. Amid different therapeutic strategies available in the clinic, chemotherapy, target therapy, and/or radiotherapy may play a possible role; however, major concerns are raised by immunomodulatory drugs, due to their intrinsic and pleiotropic effect on the functional activity of patients' immune system. Among those, immune checkpoint inhibitors (ICI) being the pillar of cancer immunotherapy in different solid tumor types worldwide, they undoubtedly represent the focus of greatest attention for their potential intersection with COVID-19 infection (**Table 1**). Unfortunately, although, no compelling scientific evidence is available yet to confirm or deny this potential relationship. Nevertheless, COVID-19 disease represents a major clinical threat for patients with cancer today, and will likely be such in the next months, if not years; therefore, some sort of guidance/recommendations are needed nowadays and prospectively, when ICI therapy represents the treatment of choice for a given patient with cancer. In this complex and dynamic clinical scenario, in spite of the paucity of scientific data, available literature evidence may help to identify a practical therapeutic algorithm for ICI therapy of patients with cancer that can

currently provide guidance to treating physicians. However, efforts will be clearly required to identify preclinical and clinical gaps and questions that need to be filled and addressed, to further unveil the potential interference of ICI therapy on COVID-19 disease in patients with cancer.

Where We Stand

First, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the agent responsible for COVID-19, is a newly identified strain of the single-stranded RNA coronavirus (CoV) family, including the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), that generated the 2002 and 2012 epidemics, respectively (1). All three strains are known to cause severe, and even fatal, lower respiratory infections. A common laboratory hallmark of these infections has been circulating lymphopenia, and SARS-CoV and MERS-CoV have specifically been shown to deplete $CD4^+$ T cells and induce T-cell apoptosis (2). In accordance with this finding, lymphopenia in SARS-CoV-2–infected patients worsens as patients clinically deteriorate and recovers as patients improve (2). Furthermore, in the early phase of COVID-19 infection, circulating T cells can express surface molecules consistent with early activation (i.e., CD38 and HLA-DR; ref. 3), and upregulate PD-1 (2). This increase in PD-1 expression may represent a marker of T-cell exhaustion on one side, although it is also consistent with phenotypic changes associated with the early phases of T-cell priming in the context of acute viral infections (4). As far as ICI, therapeutic targeting of CTLA-4 swiftly expands the $CD4^+$ and $CD8^+$ pool of T cells, while therapeutic PD-1/PD-L1 engagement reinvigorates exhausted T cells (5). Altogether, these findings seem to support the possibility that ICI treatment may contribute to counteract the immunologic impairment of T-cell number and function induced by COVID-19 infection. Thus, in one potential mechanistic scenario, ICI treatment may ameliorate the early phase of COVID-19 disease by contributing to viral clearance and also through the reactivation of $PD-1^+$ viral epitope–specific T cells (**Fig. 1A**). On the other hand, ICI therapy may instead tilt the immunologic balance, favoring COVID-19 disease worsening toward its more aggressive inflammatory late stage through the promotion of different immune-activating mechanisms (**Fig. 1A**).

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Translational Relevance

Infection by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) poses major challenges to patients with cancer and treating physicians due to the potential cross-interference of COVID-19 disease and cancer treatment with immune checkpoint inhibitors (ICI). In this specific context, literature is very limited, although available evidence can still help shed some light on the potential intersection between ICI therapy and SARS-CoV-2 infection. However, because the COVID-19 pandemic will likely represent a major concern also for the future, significant clinical and translational issues and questions will need to be addressed. Therefore, it seems useful to provide some practical guidance for today and to highlight research paths for the future.

A second piece of evidence derives from a large number of clinical trials, in which patients with solid and hematopoietic malignancies of different histologic types, and with a concomitant human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis B virus (HCV) infection, were treated with ICI. Remarkably, toxicity and efficacy rates were reported to be similar to those observed in patients without viral infection, and viral reactivation was not observed (6, 7). Of note, similar results were observed in patients with advanced hepatocellular carcinoma with HCV or HBV infection who were receiving antiviral therapy (8). On the basis of these findings, ICI therapy was concluded to be safe and effective in patients with virally related or unrelated malignancies (6–8). Notably, alike SARS-CoV-2, HIV and HCV are RNA viruses (9).

A third piece of evidence concerns the potential contribution of ICI therapy on the systemic inflammatory response to SARS-CoV-2–associated pathology that characterizes the late stage of the disease. Indeed, higher levels of circulating IL6, produced mainly by innate immune cells in response to virally mediated Toll-like receptor activation, were identified in hospitalized subjects with a more severe COVID-19 disease course (10). Also ICI therapy can be associated with increased cytokine-mediated toxicity (11); however, this does not seem to represent a significant clinical issue because in the late, inflammatory stage of COVID-19 disease the therapeutic attention is fully paid on rescuing patients from the COVID-19–induced organ failures. Conversely, ICI-mediated cytokine release may rather represent a clinical issue in the early phase of SARS-CoV-2 infection, as it may worsen the morbidity and clinical course of COVID-19 disease, as discussed above. Even in this potential occurrence, treatment with the anti-IL6 tocilizumab may help as it has been reported to improve clinical symptoms related to COVID-19 disease (12).

Present and Prospective Challenges

The retrospective evidence above and the considerations one can draw at present, seem to comprehensively point to a modest interference of ICI therapy on COVID-19 course; however, in the absence of robust clinical and laboratory data, caution must be taken in transposing these concepts "*tout court*" to our daily practice during the time of the COVID-19 pandemic. Adding complexity to this scenario is the generally unknown COVID-19 infection status of patients with cancer when initial therapeutic decisions are made or, even more challenging, when ICI therapy is ongoing (**Fig. 2**).

One could argue that to be on the safer side, chemotherapy could represent an alternative to ICI treatment. However, this quite "conservative" approach should be carefully balanced against the clinical benefit of chemotherapy compared with ICI, and toward its generally immunosuppressive activity that can be worsened when associated with radiotherapy. Furthermore, when target therapy can represent a valid alternative to ICI treatment, it could be a strategy to be pursued, although a limited percent of patients with cancer is suitable to targeted agents. The possible interference of these diverse therapeutic strategies in facilitating COVID-19 infection, or in worsening the course of disease in asymptomatic subjects who are unknown to be COVID-19 positive, remains to be fully unveiled. Answer to these questions will hopefully derive in the next months from the ongoing collections of large series of prospective data.

Table 1. Immunotherapeutic agents approved by FDA and EMA.

Tumor type	ICI	Other immunotherapies
Basal cell carcinoma	PD1	Anti-TLR7
Bladder cancer	PD1, PD-L1	BCG
Cervical cancer	PD1	None
Colorectal cancer	PD1, PD1+CTLA-4	None
Cutaneous squamous cell carcinoma	PD1	Anti-TLR3
Gastroesophageal cancer	PD1	None
Hepatocellular carcinoma	PD1	None
Head and neck cancer	PD1, PD1+CHT	None
Melanoma	PD1, CTLA-4, PD1+CTLA-4	IL2, IFNα-2b, T-VEC
Merkel cell carcinoma	PD1, PD-L1	None
MSI-H or dMMR cancer	PD1	None
Non–small cell lung cancer	PD1, PD-L1, PD1+CHT, PD-L1+CHT+anti-VEGF	None
Renal cell carcinoma	PD1, PD1+CTLA-4, PD1/-L1+anti-VEGFR	IL2
Small cell lung cancer	PD1, PD-L1+CHT	None
Triple-negative breast cancer	PD-L1+CHT	None

Abbreviations: BCG, Bacillus Calmette-Guérin; CHT, chemotherapy; CTLA-4, cytotoxic T lymphocyte antigen-4; dMMR, mismatch repair-deficient; EMA, European Medicines Agency; MSI-H, microsatellite instability-high; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TLR, Toll-like receptor; T-VEC, Talimogene laherparepvec.
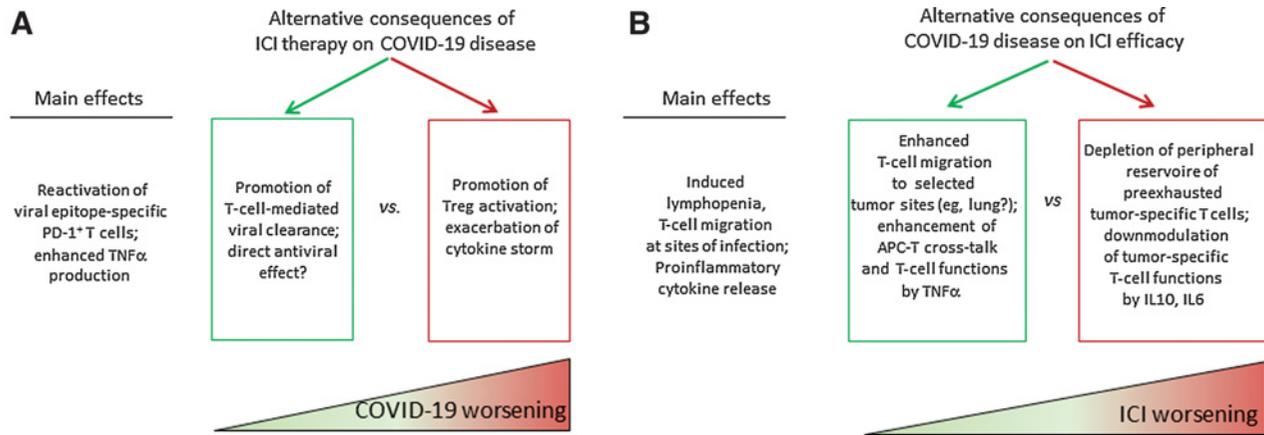
Figure 1
Landscapes of potential intersection between ICI therapy and COVID-19 disease in patients with cancer. **A,** Cancer immunotherapy by ICIs in patients infected by SARS-COV-2 could potentially impact on clinical evolution of COVID-19 disease. In the instance of PD-1/PD-L1 axis blockade, PD-1^{+} viral epitope–specific T cells may be functionally reactivated and TNFα production by such T cells could be boosted. This may lead to two opposite consequences: promotion of regulatory T-cell (Treg) activation; exacerbation of cytokine storm, rather than increasing viral clearance and possibly inducing direct antiviral effect by TNFα. **B,** Antitumor activity of ICI may be skewed in opposite directions by systemic immunologic changes due to COVID-19: SARS-COV-2–induced lymphopenia and cytokine storm could negatively impact, respectively, on the magnitude of the peripheral pool of preexhausted tumor-specific T cells and compromise the function of tumor-specific T cells; however, opposite effects cannot be ruled out, such as enhanced migration of T cells to tissues that are at the same sites of infection and of cancer growth (e.g., the lung in patients with non–small cell lung cancer treated with ICI) or TNFα-mediated promotion of APC-T cross-talk and T-cell function.

It is undoubtful that ICIs represent the ever-growing therapeutic strategy in different cancer types, in which they have received approval by regulatory agencies worldwide (**Table 1**); these increasing clinical successes make ICIs a field with the most investigated anticancer drugs, either alone or in novel combinations/sequences (13). Against this background, a further significant practical impact that COVID-19 pandemic is undoubtedly having in our referral institutions, as well as in major centers worldwide having a strong focus on clinical research, is the current pause of the very large majority of ongoing and novel ICI-based clinical trials. This adds up to the redirection, also at the expense
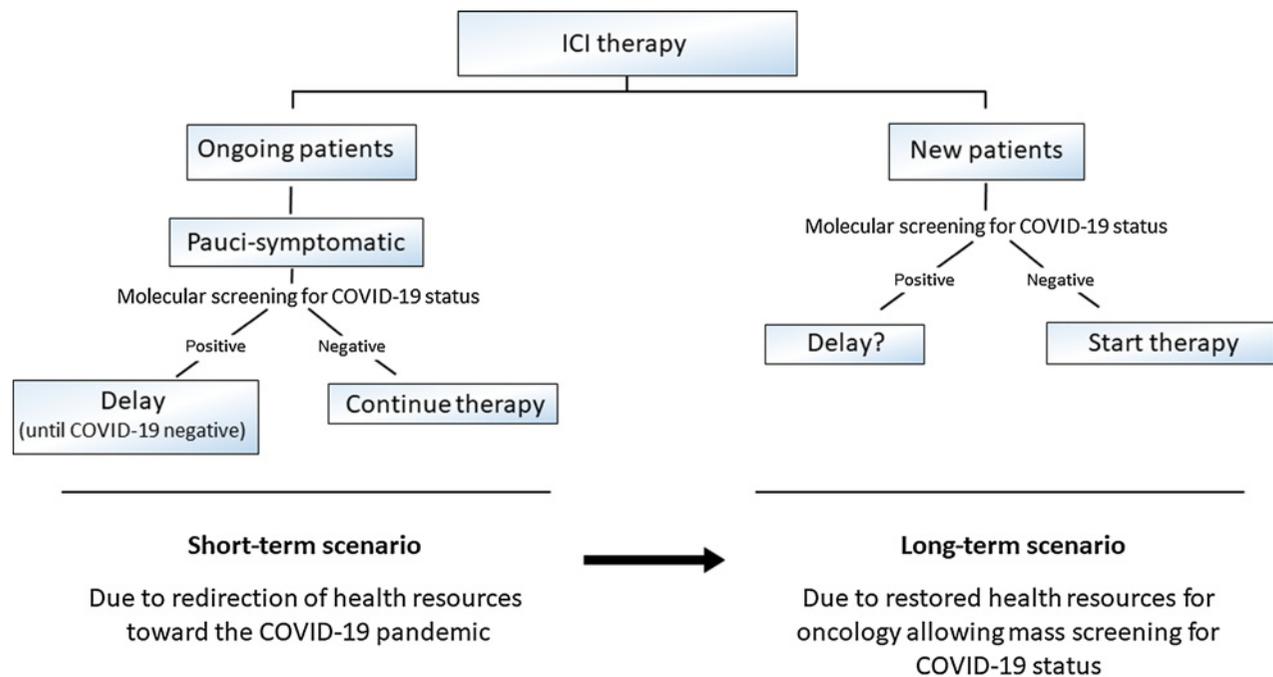
Figure 2
Current and prospective scenarios of ICI therapy in patients with cancer during the COVID-19 era.

of oncology, of health resources toward COVID-19 disease. As a comprehensive consequence, at the moment patients with cancer cannot receive treatment with novel medicines and new therapeutic combinations, which may give them more hope for cure or improved survival, as compared with standard therapies.

Thus, what can be suggested nowadays from a practical standpoint regarding ICI therapy and COVID-19 infection based on the available evidence?

From a clinical viewpoint, when ICI treatment represents the therapy of choice, it seems neither reasonable to deny it to patients with cancer nor to interrupt its administration fearing COVID-19 infection. However, closer monitoring of ICI-treated patients should be strongly recommended because of the potential development of ICI-related pneumonitis, where treatment is definitively different as compared with COVID-19 infection (14). Individual discussions with patients weighing the risk and benefit of combination versus single-agent ICI are critical given the more frequent need for immune suppression to treat toxicity with combination therapy. Elderly patients with cancer being at higher risk to develop severe COVID-19 disease, the decisions with ICI in combination should be much more judicious in this population. Furthermore, the use of ICI in adjuvant settings, which already incorporates a challenging discussion of the possibility of long-term toxicity in potentially cured patients is now even more important. In addition, screening for COVID-19 disease before ICI therapy is strongly recommended to minimize the risk of activating treatment in SARS-CoV-2–infected asymptomatic patients. Consistently, patients who develop symptoms that recall COVID-19 disease during ICI therapy should be swiftly screened for SARS-CoV-2 infection (**Fig. 2**). This strategy seems to become an increasingly feasible approach due to the availability of rapid molecular and serologic mass screening tests, and to the growing perception of the health providers that cancer is here to stay, even during the COVID-19 pandemic, and that significant resources cannot be diverted from cancer care (**Fig. 2**). On the basis of the considerations above, and from very initial observations reporting a positive outcome of COVID-19 disease in the course of ICI therapy (15), it seems reasonable to suggest/envisage a short-term therapeutic algorithm for ICI therapy during the COVID-19 pandemic, to help physicians in the decisions they are called to make every day (**Fig. 2**). However, it is imperative for the oncology community to collect prospective data on the COVID-19 status in as much as possible ICI-treated patients with cancer, also because the pandemic will not be unfortunately over for the next months to come. This will allow to interrogate in-depth the clinical intersection between ICI therapy and SARS-CoV-2 infection, building a long-term therapeutic algorithm for patients with cancer that will be most likely needed because of the forecasted persistence of COVID-19 disease worldwide (**Fig. 2**).

From a preclinical viewpoint, it seems crucial that prospective studies are designed to unveil the potential intersection of ICI therapy and SARS-COV-2 infection in the early phase of COVID-19 disease, when ICI treatment represents an unquestionable and challenging need for patients with cancer. These studies should be aimed at validating the retrospective evidence pointing to a modest interference of ICI therapy on the course of COVID-19 disease (**Fig. 1A**).

On the other hand, the possible effect of SARS-COV-2 infection on ICI-mediated antitumor immunity cannot be ruled out. Therefore, studies should also be designed to investigate the potential skewing effects of COVID-19 disease on all aspects of the cancer immunity cycle. This includes understanding how SARS-COV-2 infection

impacts the functional differentiation of circulating and tumor-associated T cells in patients with cancer, on the structure of the tumor immune contexture, on the profile of crucial chemokines that recruit distinct immune cell subsets at tumor site, and on the spectrum of proinflammatory cytokines comodulated by COVID-19 and ICI (**Fig. 1B**).

Conclusions

Although with the necessary caution, it seems reasonable to suggest that ICI therapy should not in principle be currently excluded as a therapeutic option for patients with cancer in the COVID-19 era. Thoughtful discussions within the oncology community and with patients are anyway more important than ever. Filling clinical and preclinical gaps will be mandatory to provide strong evidence-based therapeutic guidance and mechanistic insights on the possible immune intersection between COVID-19 disease and cancer therapy.

Disclosure of Potential Conflicts of Interest

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