

# Are Cancer Patients at Higher Risk of Death with COVID-19?

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel betacoronavirus that has caused more than 95,000 cases of the disease and over 3000 deaths worldwide as of early March 2020.<sup>[1]</sup> SARS-CoV-2 is spreading around the world.<sup>[2]</sup> However, the true denominator of cases remains unclear. Importantly, we know little about risk factors for severe disease or death from the current coronavirus disease (COVID-19) in immunocompromised patients. A recent nationwide analysis from China identified 18 patients with cancer who were infected by SARS-CoV-2.<sup>[3]</sup> Of these patients, 2 had unknown treatment status and, of the remaining 16, 4 had received chemotherapy or surgery within a month of the infection, and the other 4 were cancer survivors. Interestingly, 5 (28%) of the 18 were lung cancer patients. When compared to patients without cancer ( $n = 1572$ ), these patients with cancer ( $n = 18$ ) were significantly more likely to be admitted to the intensive care unit, requiring invasive ventilation, or to die (39% vs. 8%, respectively;  $p = 0.0003$ ).<sup>[3]</sup> Those patients tended to have worse respiratory disease and higher risk of death, suggesting that cancer patients infected with SARS-CoV-2 might have worse outcomes.

Cancer patients who are being actively treated with cytotoxic chemotherapies or shortly after hematopoietic stem cell transplantation often suffer from myelosuppression, leading to defects in their adaptive as well as innate immune system.<sup>[4]</sup> In this brief communication, we aim to discuss possible risk factors that may lead to worse outcomes in cancer patients and possible therapies by reviewing available data on recent SARS-CoV-2 infections, as well as the severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome (MERS)-CoV outbreaks.

SARS-CoV-2 genome's sequence is 82% similar to severe acute respiratory syndrome coronavirus (SARS-CoV-1),<sup>[5]</sup> a virus that caused an epidemic in 2002–2003, and is similar to MERS, which caused the 2012 epidemic in some Middle Eastern countries.<sup>[6,7]</sup> Coronaviruses are single-stranded enveloped RNA viruses and contain four main structures: a spike protein (S), a membrane protein (M), an envelope protein (E), and a nucleocapsid (N). These structures allow for membrane fusion with S, entry into the cell with M, and viral packaging with E and N proteins.<sup>[8]</sup> The virus infects the epithelial cells and is able to enter innate immune cells such as macrophages and dendritic cells, leading to the production of large

amount of proinflammatory cytokines and chemokines.<sup>[9]</sup>

Neutralizing antibodies against SARS-CoV-1 found in patients and animals infected with SARS-CoV block viral entry by binding to the S glycoprotein.<sup>[10]</sup> In addition to the humoral response, the role of T cells in viral infections is believed to be just as important. While neutralizing antibodies can prevent viral entry, the body also requires SARS-CoV-specific CD4<sup>+</sup> T helper cells for the development of these specific antibodies. Similarly, CD8<sup>+</sup> cytotoxic T cells are important for the recognition and killing of infected cells, particularly in the lungs of infected individuals. The epitopes of the S and N proteins become highly immunogenic and produce robust CD8<sup>+</sup> T cell-mediated responses. These responses also have been shown to be durable and produce memory responses.<sup>[11]</sup> Therapies that hinder humoral immunity by eliminating B cell function, such as rituximab for various lymphomas, as well as T cell function, as in cytotoxic chemotherapies, may put these patients at a significantly higher risk of deleterious effects from COVID-19 infection. Previous data from MERS and SARS infections show that early CD8<sup>+</sup> T cell responses are directly related to infection severity.<sup>[12,13]</sup> Additionally, in patients who are elderly and who have existing lung disease, there is a higher risk of infection.<sup>[14]</sup> This higher risk could be extrapolated to our patients with cancer, who should also be considered at high risk for worse outcomes from SARS-CoV-2. These patients especially include lung cancer patients, as described in a report from China for patients with COVID-19 and cancer,<sup>[3]</sup> and patients with metastases to the lungs, radiation-induced lung injury or interstitial lung disease, or pneumonitis from checkpoint inhibitors. In addition, patients with hematologic malignancies and/or who are undergoing T cell-depleting therapies or who are on immunosuppression postallogeic hematopoietic cell transplantation, for example, may be at significant risk of acquiring the infection as well as progressing to a severe infection. With this in mind, it is reasonable to suggest that new therapies, such as viral protease inhibitors and other strategies, such as vaccination or monoclonal antibodies, be investigated in the most susceptible patients at risk for fatal outcomes.

There are ongoing trials with remdesivir, previously developed for the Ebola epidemic, as well as trials to repurpose HIV inhibitors, lopinavir/ritonavir, and other viral protease inhibitors.<sup>[15]</sup> There is a paucity of data relating to tyrosine kinase inhibitors (TKIs) and their activity on SARS, MERS, and COVID-19; however, there is evidence that certain TKIs may be active against these viruses, but this type of therapy would be experimental at best.<sup>[16–18]</sup> Some TKIs, however, may cause myelosuppression, albeit in a minority of patients, and this side effect could obviate any potential benefit. There are as yet, to our knowledge, no published data on TKIs for COVID-19, nor are there data about the role or impact that immune checkpoint blockade may play in suscep-

tibility to contracting the virus, severity of the disease, or potential treatment. There are more than 80 clinical trials pending or ongoing that are testing a variety of agents in hopes of finding a potent viral inhibitor with a minimal adverse profile.<sup>[19]</sup> Whether there is a role for immunotherapy, where the immune response is stimulated and infected cells may be more vulnerable, needs to be determined in future trials for patients with severe COVID-19 infections.<sup>[20]</sup>

We propose several major strategies for patients with cancer in this COVID-19 epidemic and in future epidemics with emergent pathogens that may be highly transmissible and/or cause severe infections. First, personal protection should be emphasized for patients with cancer on active therapy or for cancer survivors. Second, more intensive surveillance or treatment should be considered when patients with cancer are infected with SARS-CoV-2, especially older patients or those with other comorbidities.<sup>[3]</sup> Extra vigilance to protect patients with cancer is reasonable.

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