### Title

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# 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 and over 3,000 deaths worldwide as of early March 2020.[1] SARS-CoV-2 is spreading around the world.[2] 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 afflicted with cancer who were infected by SARS-CoV-2.[3] Of these patients, two had unknown treatment status and, of the remaining 16, four had received chemotherapy or surgery within a month of the infection, and the other four were cancer survivors. Interestingly, five (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).[3] 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 on active treatments with cytotoxic chemotherapies or early after hematopoietic stem cell transplantation often suffer from myelosuppression leading to defects in their adaptive as well as innate immune system.[4] 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)[5], which caused an epidemic in 2002-2003 and similar to MERS that caused the 2012 epidemic in some Middle Eastern countries.[6,7] Coronaviruses are single-stranded enveloped RNA viruses and contain 4 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.[8] The virus infects the epithelial cells, and able to enter innate immune cells such macrophages and dendritic cell, leading to the production of large amount of pro-inflammatory cytokines and chemokines.[9]

Neutralizing antibodies against SARS-CoV-1 found in patients and animals infected with SARS-CoV block viral entry by binding to the S glycoprotein.[10] Besides the humoral response, the role of T cells in viral infections is believed to be just as important. Whilst neutralizing antibodies can prevent viral entry, the body also requires SARS-CoV specific $CD4^+$ T helper cells for the development of these specific antibodies. Similarly, $CD8^+$ 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 $CD8^+$ T cell-mediated responses. These responses have been shown to also be durable and produce memory responses.[11] 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 significantly higher risk of deleterious effects from COVID-19 infection. Previous data from MERS and SARS infection show that early CD8+ T cell responses are directly related to infection severity.[12,13] Additionally, in patients who are elderly and with existing lung disease, there is a higher risk of infection.[14] This higher risk could be extrapolated to our patients with cancer that should also be considered at high risk for worse outcomes from SARS-CoV-2, and includes especially lung cancer patients as described in a report from China for patients with COVID 19 and cancer[3] or patients with metastases to the lungs, those that have radiation-induced lung injury or interstitial lung disease or pneumonitis from checkpoint inhibitors. In addition, patients with hematologic malignancies and/or undergoing T-cell depleting therapies or on immunosuppression post-allogeneic 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.[15] 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.[16-18] However, some TKIs may cause myelosuppression, albeit in a minority of patients, and this side effect could obviate any potential benefit. There are yet no published data on TKIs for COVID-19 nor is there data about the role or impact that immune checkpoint blockade may play in susceptibility to contracting the virus, severity of the disease, or potential treatment. There are more than 80 clinical trials pending or ongoing testing a variety of agents in hopes to find a potent viral inhibitor with minimal adverse profile.[19] 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.[20]

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 causing severe infections. First, personal protection should be emphasized for patients with cancer on active therapy or cancer survivors. Second, more intensive surveillance or treatment should be considered when patients with cancer are infected with SARS-CoV-2,

especially in older patients or those with other comorbidities.[3] Extra vigilance to protect patients with cancer  is reasonable.

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