Brief Communication

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.[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 with cancer who were infected by SARS-CoV-2.[3] 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; $p = 0.0003$).[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 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.[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] a virus that caused an epidemic in 2002–2003, and is similar to MERS, which caused the 2012 epidemic in some Middle Eastern countries.[6,7] 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.[8] 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.[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] 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 $CD4^+$ 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 also have been shown to 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 a significantly higher risk of deleterious effects from COVID-19 infection. Previous data from MERS and SARS infections show that early CD8+ T cell responses are directly related to infection severity.[12,13] Additionally, in patients who are elderly and who have existing lung disease, there is a higher risk of infection.[14] 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,[3] 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 postallogeneic 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] 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 susceptibility 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.[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 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.[3] Extra vigilance to protect patients with cancer is reasonable.

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References

1. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report–45. https://wwwwhoint/docs/default-source/coronaviruse/situation-reports/20200305-sitrep-45-covid-19pdf?sfvrsn=ed2ba78b_2. Published March 6, 2020. Accessed March 6, 2020.
2. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020 Feb 24 [Epub ahead of print]. DOI: https://doi.org/10.1016/S2213-2600(20)30079-5.
3. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21:335–337.
4. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell*. 2015;28:690–714.
5. Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect*. 2020;9:221–236.
6. Aleanizy FS, Mohmed N, Alqahtani FY, El Hadi Mohamed RA. Outbreak of Middle East respiratory syndrome coronavirus in Saudi Arabia: a retrospective study. *BMC Infect Dis*. 2017;17:23.
7. Fauci AS, Lane HC, Redfield RR. Covid-19–Navigating the uncharted [editorial]. *N Engl J Med*. February 28, 2020. doi:10.1056/NEJMe2002387.
8. Siu YL, Teoh KT, Lo J, et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. *J Virol*. 2008;82:11318–11330.

9. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol*. 2015;1282:1–23.
10. Hsueh PR, Huang LM, Chen PJ, Kao CL, Yang PC. Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. *Clin Microbiol Infect*. 2004;10:1062–1066.
11. Janice Oh HL, Ken-En Gan S, Bertoletti A, Tan YJ. Understanding the T cell immune response in SARS coronavirus infection. *Emerg Microbes Infect*. 2012;1:e23.
12. Shin HS, Kim Y, Kim G, et al. Immune responses to Middle East respiratory syndrome coronavirus during the acute and convalescent phases of human infection. *Clin Infect Dis*. 2019;68:984–992.
13. Li CK, Wu H, Yan H, et al. T cell responses to whole SARS coronavirus in humans. *J Immunol*. 2008;181:5490–5500.
14. Gorse GJ, Donovan MM, Patel GB, Balasubramanian S, Lusk RH. Coronavirus and other respiratory illnesses comparing older with young adults. *Am J Med*. 2015;128:1251, e1211–1220.
15. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol*. 2020. DOI: 10.1038/d41587-020-00003-1.
16. Shin JS, Jung E, Kim M, Baric RS, Go YY. Saracatinib inhibits Middle East respiratory syndrome-coronavirus replication in vitro. *Viruses*. 2018;10. DOI: 10.3390/v10060283.
17. Coleman CM, Sisk JM, Mingo RM, Nelson EA, White JM, Frieman MB. Abelson kinase inhibitors are potent inhibitors of severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus fusion. *J Virol*. 2016;90:8924–8933.
18. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395:e30–e31.
19. Maxmen A. More than 80 clinical trials launch to test coronavirus treatments. *Nature*. 2020;578:347–348.
20. Adashek JJ, Junior PNA, Galanina N, Kurzrock R. Remembering the forgotten child: the role of immune checkpoint inhibition in patients with human immunod eficiency virus and cancer. *J Immunother Cancer*. 2019;7:130.