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Systemic Treatments: Is it making Cancer Patients more Vulnerable to COVID 19?

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Abstract

COVID 19 caused by SARS-CoV-2 has spread across the globe claiming millions of life. However, many have survived after infection. There are multiple risk factors associated with the fatality of the disease like age, immunity, gender, diabetes, organ transplantation etc. Host immune response plays a critical role in control of infection and pathogenesis during this viral infection. Any treatment that modulate host immune response should be critically analysed before its implementation during this pandemic. Cancer patients receive systemic treatments to regress the tumor growth and have multiple side effects on host immune response. Little is known about the impact of such anticancer treatments on vulnerability, severity and mortality from COVID 19. This mini review focuses on the current literature and highlights the probable increase in risks for cancer patients receiving systemic anticancer treatments during the COVID-19 pandemic.

Keywords: Covid 19; Cancer; Systemic treatments; Immune response; Risk factor.

Introduction

COVID 19 is caused by a novel enveloped RNA beta-coronavirus that is currently known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, also called 2019-nCoV).[1] Inhalation of novel coronavirus latches the viral particles through angiotensin-converting enzyme 2 (ACE2) receptor onto the host cells that infiltrate the upper portions of the respiratory tract damaging it.[2] In response, host adaptive and cell mediated immune system play critical role in clearing off the virus reducing the severity of infection.

Infection with SARS-Cov-2, is assumed to function in tandem with a myriad of health challenges faced by treatment receiving cancer patients as host immune response is most critical in deciding the survival of COVID 19 patients. Most of the systemic cancer treatments trigger multiple molecular signalling pathways effecting immune system. According to a study, conducted on 414 randomly recruited patients with confirmed COVID-19 in Renmin Hospital of Wuhan University, abnormal cellular immunity and humoral immunity were key features of non-survivors with COVID-19.

Neutrophilia, lymphocytopenia, low $CD4^+$ T cells, and decreased C3 were immunity-related risk factors predicting mortality of patients with COVID-19.[3] Hence, weak immunity increases the severity of infection and rate of mortality. To understand the manifestation of COVID-19 in cancer patients that are receiving immune modulating systemic treatments, we must address the probable impact of these treatments on pathogenesis of coronavirus disease.

Immune Response during SARS-Cov-2 infection

COVID 19 is caused by inhalation of fine droplets containing SARS-CoV-2. Efficient immune system senses the viral challenge to protect the host. To defend tissue against any inhaled pathogen, the airways is not only endowed with physical barriers such as a mucus layer over its entire surface, but also a vast network of respiratory tract epithelial cells, dendritic cells (DC) and alveolar macrophages. These cells trigger pro-inflammatory downstream immune responses in the presence of viral particles recruiting more innate and adaptive immune cells to limit pathogen spread. Type of immune cells recruited and polarization of immune response decide the severity of any infection like depletion of tissue-resident alveolar macrophages in broncho-alveolar lavage cells has been reported to be associated with disease severity.

Thus any cancer treatment that reduces their count can lead to increased severity of viral infection making patient more vulnerable to Covid 19. T cells play pivotal role in generating immune response against multiple cancers (Table.1) and controlling coronavirus infection. According to a recent study, conducted on COVID patients, non survivors had smaller lymphocyte count (0.69 × 109 /L vs 1.20 × 109 /L), diminished T cells subsets [CD3+ T cells (277 vs 814 cells/µl), CD4+T cells (172 vs 473 cells/µl), CD8+ T cells (84 vs 262.5cells/µl, $P < 0.001$), CD19+ T cells (88 vs 141 cells/µl) and CD16+ 56+ T cells (79 vs 128.5 cells/µl) ($P < 0.001$)] when compared to survivors of COVID 19.[3] This study, strongly indicates the protective role of lymphocytes especially T cells in controlling of SARS-CoV-2 infection during COVID 19 pathogenesis.[5,6]

Taken together, this clearly indicates that immunosuppressive agents/treatments that suppress lymphocyte cell count, especially T cells, may be particularly detrimental in fighting COVID-19, and thus should be avoided in patients with cancer. This review will shed light on probable effect of systemic anticancer treatments on patients vulnerability to develop coronavirus infection, rate of its severity and mortality caused due to it.

Anti cancer systemic treatments

Radiotherapy

Radiotherapy is a systemic treatment given to cancer patients to regress tumor growth. Radiation used in this therapy cannot differentiate between cancer cells and healthy cells. That's why it even hampers number of immune cells like lymphocytes (T cells, B cells and NK) which are among the most radiosensitive cells, followed by monocytes, macrophages and antigen-presenting cells (APCs), specifically dendritic cells (DC), which have comparatively higher radio resistance.[7-9] This treatment therefore leads to weakened host immunity. As lymphocytopenia act as markers of high death risks of patients with COVID-19, such treatments should be avoided during pandemic.[10,11] Lymphocytes especially T cells help in fighting against this viral infection as their number are higher in survivor as compared to non survivors of COVID 19.[3]

The protective role of T cells in SARS-CoV-2A can be well understood by a study that revealed that genes involved in T cell activation and function, such as MAP2K7 and SOS1 are downregulated in the T cells of severe COVID-19 patients and their expression of these genes returned to normal levels upon recovery.[12] Therefore, treatments like radiotherapy that lower patient's T cells, macrophages or monocyte count make cancer patients more vulnerable to COVID 19 and decreases their chances of survival once infected.

Chemotherapy

Chemotherapy is another one of the common treatment for cancer. Chemotherapy drugs are designed to target rapidly and uncontrollably dividing cancer cells preventing them from growing further. Different combinations of medications are used depending upon the type of cancer as part of a chemotherapy treatment plan. Cancer patients receiving chemotherapy have significantly lower WBC leading to neutropenia making it difficult to fight off viruses, bacteria, and other pathogens. This means the risk of infection is high. Patients with cancer are known to be at an increased risk for community acquired respiratory viruses, such as influenza, due to their frequently observed immunocompromised state.[13]

High fatality due to SARS-CoV-2 infection has been observed with cancer patients in Wuhan due to weakened immune response.[14,15] One of the reasons for increased risk of infection is non-targeted systemic treatment that do not distinguish between cancer and normal cells including immune cells.

Immunotherapy

One of the latest techniques used to treat cancer is immunotherapy where the patients' immune

system is boosted and trained to either slow or slop or destroy cancer cells. Immunotherapy is therefore very useful in treatment of many types of cancer. Immunotherapy include multiple approaches to treat cancer patients like T cell therapy, Monoclonal antibodies and tumor-agnostic treatments, such as checkpoint inhibitors etc. Unlike conventional methods like radiotherapy and chemotherapy, immunotherapy is targeted and improves immune response rather than impeding immunity. Thus, immunotherapies initiates a self-sustaining attack against cancer cells by host immune cells that produces long-term clinical benefits, or even a cure.

According to American Association for Cancer Research (AACR) 2020 Virtual Meeting: COVID-19 and Cancer, treatment with immune checkpoint inhibitors (ICIs) do not increase the risk of mortality in patients with COVID-19 and cancer. According to the article that was originally published on OncLive as, "Immunotherapy Use Does Not Correlate With Increased Mortality in Patients with COVID-19, Cancer." and was presented at: 2020 AACR Virtual Meeting: COVID-19 and Cancer; July 20-23; mortality rate of cancer patients with COVID-19 is almost same for individuals who received or did not receive immuno-oncology agents i.e., nearly 8%. Immunotherapy in combination with conventional treatments could be a better option for serious cancer patients during COVID 19. Combination therapy will not hinder host immune response as much as chemo or radiotherapy when used alone. This will help cancer patients to better fight against SARS-CoV-2A in case of infection and reduce the rate mortality in such patients.

Table 1: Protective role of immune cells in multiple cancers.

Type of Cancer	Crucial Immune Cells	Treatment That Can Hamper Immune Cells That Trigger Anti Cancer Response
Skin Cancer	Anti-tumour immune-surveillance is done by members of the adaptive immune system- B and T lymphocytes. Impedance in T cells' count or activation or proliferation is associated with tumor progression.[16-20]	Yes
Lung Cancer	Key immune cells involved in the pathogenesis of lung cancer include CD4+ T-lymphocytes, macrophages, dendritic cells, and natural killer cells.[21]	Yes
Breast Cancer	CD8+ T cells, CD4+ Th1 cells, NK cells, B cells, classically activated macrophages (M1), and mature dendritic cells contribute to tumor elimination.[22]	Yes
Colorectal Cancer	T cells in colorectal cancer (CRC) are associated with improved survival. Macrophages are associated with favourable prognosis.[23]	Yes
Kidney Cancer	numerous subpopulations of activated, memory-like, type 1-differentiated T cells are recruited and in some cases clonally expanded at the tumor site in Renal cell carcinoma (RCC) patients.[24]	Yes
Bladder Cancer	both innate and adaptive immune cell populations play critical role in generating immune response against cervical cancer.[25]	Yes

Conclusion

Few studies arising from China, have reported that cancer patients receiving systemic anticancer treatments have higher risk of disease development compared their counterparts who are not receiving anticancer treatment.[26-28] Wise choice of treatment for cancer patient is therefore of utmost importance because immunity plays a critical role in deciding the risk factor against SARS-CoV-2A infection. Systemic treatments that are non-targeted, can increase mortality rate in cancer patients especially during COVID 19 pandemic. Targeted immunotherapy either used alone or in combination could be better option because it not only boosts host immunity to stop or destroy cancer growth but also reduces the chances of mortality due to SARS-CoV-2A infection.

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