Short Communication

Are COVID-19 Survivors Likely to be Better Poised to Prevent Cancer or to Cope with it ? — A Contesting Viewpoint

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The global community was witnessing a new World War, quite distinct from the World War I and World War II. The battle against the whole human race was waged by a tiny RNA virus – named SARS-CoV-2. The disease it causes is named COVID-19. First identified in Wuhan province of China in December, 2019, the disease had been spreading like a wild fire almost all around the globe. The World Health Organization declared it a pandemic on 11th March, 2020. The disease has an incubation period of 3-7 days and the longest time from infection to symptoms is 12.5 days (95% CI, 9.2 to 18)[1]. The infection has a high transmission rate; on an average, an infected person transmits the infection to an additional 2.2 individuals[2]. The size of infected cohort in this novel epidemic is known to be doubled about every 7 days. In just around 100 days, SARS-CoV-2 has already affected more than 120 million people in 210 countries, and has claimed more than 2.6 million lives. Described as the worst ever crisis the human civilization had confronted with, it had caught the modern medicine and healthcare system unaware and clueless. Though we have vaccines now to fight against the epidemic, but mutating strains are the major concerns for scientists. Second wave of the epidemic already started devastating a few countries and India is in the verge of it.

The case fatality rate of SARS-CoV-2 infection albeit relatively low – around 3 per cent, as compared to SARS-CoV-1 or MERS-CoV, its high transmission rate translating to the huge absolute number of deaths, has been the real cause of concern. The severity and death in COVID-19 is attributed to a deadly uncontrolled systemic inflammatory response – a cytokine release syndrome (CRS) and cytokine storm, causing acute respiratory distress syndrome (ARDS). There is release of large amounts of pro-inflammatory cytokines (IFN-á, IFN-ã, IL-1â, IL-6, IL-12, IL-18, IL-33, TNF-á, TGFâ, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc) by immune effect or cells in severe COVID-19 patients. High levels of pro-inflammatory cytokines lead to shock and end-organ damage, specifically Acute Respiratory Distress Syndrome (ARDS). Autopsy findings suggest evidence of tissue necrosis and interstitial macrophage and monocyte infiltrations in the lung, heart and gastrointestinal mucosa, signifying elevated inflammatory cytokines[3,4]. In critical COVID-19 patients, it is commonly seen that they have severe lymphopenia with hyper activated pro-inflammatory T cells[5] and decreased T-reg cells[6].

Many risk factors have been recognized that might increase the susceptibility as well as the vulnerability to SARS-CoV-2 infection and the poor prognosis of COVID-19. Cancer in general is believed to adversely affect the outcome in COVID-19 patients. One study showed prevalence of cancer was 1% (95% confidence interval, 0.61%-1.65%) among COVID-19 patients in China[7], whereas another suggested that the pooled prevalence of cancer was 2.0% (95% CI, 2.0%-3.0%). These data came from a meta-analysis of 11 reports including 3,661 COVID-19 cases[8]. On the other hand, to the best of our knowledge nothing is yet known how SARS-CoV-2 infection can affect different malignancies, in terms of their covert and overt progression. We herewith put forward our viewpoint based on our understanding of how the SARS-CoV-2 infection modulates the innate and adaptive immunity in humans.

Treatment modalities in cancer are evolving and immunotherapy is today addressed as the fifth pillar of cancer care, after surgery, radiotherapy, cytotoxic chemotherapy and molecular targeted therapy[9]. Chimeric Antigen Receptor (CAR) T-cell is a developing Cancer Immuno-therapy. After collecting a patient's own immune effector cells like T cells or NK cells, these are genetically engineered to express a chimeric antigen receptor which recognize a tumor-related target, expanded in vitro, and then reinfused to produce responses. This therapy prevents progression in a variety of malignancies[10]. In 2010, the first report of CAR T-cell therapy was published, in a patient with

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advanced follicular lymphoma; after infusion of CAR T-cells engineered to target CD19 protein, there was dramatic regression of lymphoma[11]. Beneficial effects were seen in acute lymphoblastic leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), and many types of non-Hodgkin lymphoma (NHL)[10]. CAR T Cell therapy is associated with a dreadful adverse effect – the CRS. It is due to results of large amounts of cytokines, including IL-6 and interferon ã rapid release into the bloodstream by activated CAR T-cells[12]. Clinical trials have shown very promising results in end-stage patients of acute lymphocytic leukemia with a full recovery of up to 92%[13].

At this juncture the questions that intrigue us are, whether the patients who recovered from the cytokine storm will be less susceptible to some cancers in future, and whether the patients' micro-cancer cells can be damaged by this virus-made disaster. We make an attempt here to find an empiric answer to these questions, in the backdrop of the apparent analogy of immunopathogenesis of COVID-19 (as described above) and the rational basis of cancer immunotherapy.

The basis of cancer immune-therapeutics is activation of Cytotoxic T Lymphocytes (CTL) to kill the cancer cells. The T regulatory (T-reg) cells help cancer cells to be saved from the attack of CTLs. In severe COVID-19, the activity of T-reg cells is found to be decreased. The CTL-associated antigen 4 (CTLA 4) and programmed cell death protein 1 (PD1) are important negative regulators of T cell immune function. Immune check point inhibitors (ICI) like CTLA 4 inhibitors (namely, ipilimumab) and PD1 inhibitors (namely, pembrolizumab), are known to increase anti-tumor immunity and have durable clinical response. As they block CTLA 4 and PD1, the CTLs become activated, and the interaction of co-stimulatory receptor and ligand in antigen presenting cell (APC) is enabled. This makes the cancer cells more susceptible to be destroyed by immune cells. CTLA 4 inhibitors also help to inhibit T-reg cells mediated suppression of CTLs. CTLA 4 inhibitors are successfully used in non-small cell and small cell lung cancers, Hodgkin lymphoma, bladder cancer, renal cell carcinoma, melanoma, and Merkel cell carcinoma[14]. The ICIs also carry the risk of pneumonitis and cytokine storm and the mechanism is same like COVID-19. IL 6 inhibits T-reg cell differentiation via CD4 T lymphocyte modulation, and increases cytotoxic T lymphocyte proliferation via CD8 T cell stimulation[15]. Given the fact that IL-6 is a cytokine with its multi-faceted, non-specific immune-modulatory role in humans, it may not be too far-fetched to assume that it can confer some immunity to development of or progression of cancer. To examine this hypothesis, we recommend conduct of well-designed prospective, observational study with three matched (in terms of cancer risk factors) cohorts – one critical COVID-19 survivors, one non-critical COVID-19 patients after recovery, and another non-COVID-19 participants, and following them up for assessing the relative risk of cancer among them. One can also take up cancer genomics research in suitable animal models like with knockout mice for the genes involved in cancer regulation.

All crises bring with them a host of opportunities. We need to think through the crisis of COVID-19, particularly the molecular basis of its immune-pathogenesis and manifestations and understand its nature thoroughly. May be, we shall be rewarded with the much sought-after solution to the problem of cancer immuno-modulation.

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