Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Editorial
Volume 20 Issue 2 - December 2021
DOI: 10.19080/CTOIJ.2021.20.556035

Cancer Ther Oncol Int J

COVID-19 and Cytokine Storm

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Submission: November 24, 2021; **Published:** December 07, 2021

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Abstract

Cytokine storm has no definition. It is a condition that describes uncontrolled systemic hyper-inflammation occurring in many diseases, such as malignancy, rheumatologic disease, sepsis syndrome and COVID-19 infection. The novel coronavirus causes respiratory problems as well as damage of the heart, kidneys, liver, and other organs. Excess cytokines produced in COVID-19 infections leads to multiple-organ failure and even death. Evaluating a patient with cytokine storm should achieve the following goals: rule out other disorders that may mimic cytokine storm, identify the underlying disorder, establish its severity, and determine the clinical trajectory.

Abbreviations: Ang II: Angiotensin II; AT1R: Ang II type 1 receptor; ARDS: Acute Respiratory Distress Syndrome; ACE2: Angiotensin Converting Enzyme-2

Introduction

Cytokine storm has no definition [1]. It is a state of accentuated uncontrolled systemic hyper-inflammation [2] that results from a complex, interconnected network of cell types, signaling pathways, and cytokines [3]. Interferons, interleukins, tumor-necrosis factors, chemokines and several other mediators are released in excess [1]. The key cytokines that thought to have central immunopathologic roles and are injurious to host cells in cytokine storm are interferon-γ, interleukin-1, interleukin-6, TNF, and interleukin-18 [3]. Most mediators implicated in cytokine storm demonstrate pleotropic downstream effects and are frequently interdependent in their biological activity [1]. It occurs in malignancy, rheumatologic disease, sepsis syndrome and COVID-19 infection [2].

IL-6 amplifier: machinery for excessive inflammation

The temporary failure of the immune response in the initial period of SARS-CoV-2 infection induces excessive late immune response to compensate for failure of the virus clearance. This causes severe form of COVID-19 generalized hyper-inflammation in lung that leads to acute lung injury and acute respiratory distress syndrome (ARDS) [2].

SARS-CoV-2 enters the body by targeting angiotensin converting enzyme-2 (ACE2) receptor on alveolar type 2 cells in the lungs [2]. SARS-CoV-2 infection induces endocytosis of ACE2 and SARS-CoV in target epithelial cells and endothelial cells. This will increase serum level of angiotensin II (Ang II). Ang II acts as a pro-inflammatory cytokine via Ang II type 1 receptor (AT1R). Ang II-AT1R signaling creates an IL-6-mediated positive feedback loop of NF-κB signaling. This mechanism is known as IL-6 amplifier. The IL-6 amplifier is a hyper NF-κB activation machinery in non-immune cells induced by coactivation of NF-κB and STAT3. Massive sustained production of IL-6, chemokines, and growth factors (NF-κB target genes) will occur. Activation of IL-6 amplifier depends on NF-κB stimulators and IL-6 concentrations in non-immune cells. Activation occurs more easily in tissue-specific non-immune cells such as tracheal basement cells, synovial fibroblasts, keratinocytes, kidney tubule cells, and chondrocytes. These cells through the IL-6 amplifier could regulate several tissue specific-inflammatory diseases [3].

Clinical Manifestations of Cytokine Storm

Cytokine storm is one of the major causes of multiple-organ failure in COVID-19 infections [4]. The novel coronavirus causes respiratory problems as well as damage of the heart, kidneys, liver, and other organs [2]. Clinical manifestations of cytokine storm often overlap in late stage [2].

Patients with cytokine storm may present with

- Fever in nearly all patients. The fever may be high grade in severe cases [5].
- Fatigue, anorexia, headache, rash, arthralgia, myalgia, diarrhea, and neuropsychiatric manifestations resulting from cytokine induced tissue damage or immune cell–mediated responses or acute-phase physiological changes [5].
- Respiratory symptoms such as cough and tachypnea that progress to ARDS, with hypoxemia requiring mechanical ventilation [5].
- Cardiac damage including irregular heart rhythm, myocarditis and pericarditis. Cardiac injury occurs in patients with underling cardiac disease or even in patients with no previous history of heart disease [4].
- Renal injury in the form of renal tubules hypoperfusion together with increased vascular permeability and cardiomyopathy that may progress to cardiorenal syndrome type 1. A condition of pleural effusion, edema, intravascular fluid depletion and hypotension [4].
- Renal failure, acute liver injury or cholestasis, and a stress related or takotsubo-like cardiomyopathy in severe cytokine storm [5].
- Neurologic manifestations several days after the onset of the cytokine storm [5].
- Capillary leak syndrome and anasarca resulting from renal dysfunction, endothelial-cell death, and acute-phase hypoalbuminemia [5].
- Spontaneous hemorrhage because of hyperinflammation, coagulopathy, and low platelet counts [5].
- Rapid progression to disseminated intravascular coagulation with vascular occlusion or catastrophic hemorrhages, dyspnea, hypoxemia, hypotension, hemostatic imbalance, vasodilatory shock and death [5].

Prognosis

Severity or mortality of cytokine storms depends on ARDS triggered by viral lung infection [3]. The human lungs will be destroyed through cytokine storms leading to hyperinflammation which force the immune cells to destroy healthy cells. The inflammatory cytokines, particularly, IL-6 released during COVID-19 infection cause the liver to produce proteins that defend the body from infections. These proteins can cause microthrombi in the lungs, lower limbs, hands, brain, heart, liver, and kidneys. Deprivation of these organs of oxygen and nutrients will lead to multiorgan failure and consequent progression to acute lung injury, acute respiratory distress syndrome, and often death [2]. Another reason of multiorgan failure is SARS-CoV-2 infection of endothelial cells which causes cell death, vascular leakage and a cytopathic effect on airway epithelial cells. The inflammatory mediators stimulate endothelial cells expressing ACE2 on arteries and veins together with viral particles to cause systemic inflammation and lead to vascular hyperpermeability [3].

Laboratory Findings

Differences in hematological, biochemical, inflammatory, and immune biomarkers between patients with or without severe disease could identify predictors of severe and fatal cases [6]. A significant hyperferritinemia (no cut-off value), in the presence of typical clinical features are suggestive of early diagnosis of cytokine storm in COVID-19 [2]. Lymphopenia, thrombocytopenia, neutrophilia and high levels of ferritin, D-dimer, aspartate aminotransferase, lactate dehydrogenase, C-Reactive Protein, procalcitonin and creatinine are good indicators of both severe and fatal cases of COVID-19 during the first days from the onset of illness [6]. Changes in circulating cell counts are most likely due to the interplay between cytokine-induced changes in production and mobilization of cells from the bone marrow, chemokine induced migration, and immune-mediated destruction [5].

Prominent elevations in serum inflammatory cytokine levels, such as interleukin-6 (the main cytokine in cytokine storm) as well as interferon-γ (or CXCL9 and CXCL10, chemokines induced by interferon-γ), interleukin-10, and soluble interleukin-2 receptor alpha (T-cell activation marker) are usually present [5]. IL-6 had higher concentration in the afternoon than in the morning. This diurnal variation in IL-6 level must be considered in the diagnosis of cytokine storm and when determining the appropriate time of administration of cytokine-targeted therapy [2].

Possible therapeutics for COVID-19

Therapies of cytokine storm triggered by SARS-CoV-2 infection may differ from those used in cytokine storm due to other causes. Cytokines are a key component of the cytokine storm and are an essential factor in the antimicrobial response. Blocking cytokine signaling may impair SARS-CoV-2 clearance, leading to increase of the risk of secondary infections and worse outcomes [5]. It is important to use the right treatment in the right selected patient [5]. Anti-inflammatory treatments are also evaluated in COVID-19 induced cytokine storm to reduce inflammation-induced damage of the respiratory tract as high inflammation is the primary cause of pathology in COVID-19 [6].

The following have been tried in COVID-19 induced cytokine storm

- **IL-6 inhibitors** have shown encouraging effects in reducing severity and mortality in severe COVID-19 [2].
- **IL-1 receptor antagonist** reduced the need for mechanical ventilation and mortality without reported serious side-effects in COVID-19. Further validation is still required [2].

How to cite this article: Nahla A M H. COVID-19 and Cytokine Storm. Canc Therapy & Oncol Int J. 2021; 20(2): 556035.
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➢ **Targeting TNF-α** is a possible therapeutic option in COVID-19 cytokine storm accompanied by lung injury [2].

➢ **JAK inhibitors** can target multiple cytokine–receptor pairs simultaneously [5]. It can impede the entry and proliferation of SARS-CoV-2. This may reduce the rate of ICU admission and fatality [2].

➢ **Glucocorticoids** have excellent immunosuppressive and anti-inflammatory effects by inhibiting production of major inflammatory molecules, including prostaglandins and leukotrienes [2]. It is suggested that glucocorticoids showed a good response in COVID-19 patients who had high CRP level and a poor response when its level is low [5].

➢ **Colchicine** impedes neutrophil's function and inhibits IL-1ß activity by inhibiting the inflammasome complex [2].

➢ **Stem cell therapy** may help immune cells differentiation [2].

➢ **Low-dose radiation therapy** (usually < 1.0 Gy) change immune cells into an antiinflammatory phenotype in severe COVID-19 [2].

➢ **Liposomes or synthetic nanoparticles** modulate macrophage dysfunction. Their use requires substantial clinical data [2].

➢ Use of **therapeutic plasma exchange (TPE)** in severe COVID-19 could be beneficial when initiated early in diagnosis based on high inflammation parameters such as serum ferritin and high-sensitivity cardiac troponin I [2].

➢ **QTY Code-Designed Detergent-Free Chemokine Receptors:** The QTY code modified transmembrane proteins is a novel synthetic protein modification tool similar in its structure to antibodies. These proteins when injected into the body bind the excess cytokines created by the cytokine storm [4].

Conclusion

Cytokine storm is one of the major causes of multiple-organ failure in COVID-19 infections. Treatment of cytokine storm triggered by SARS-CoV-2 infection may differ from that used in cytokine storm due to other causes. Cytokines are a key component of the cytokine storm. Blocking cytokine signaling may impair SARS-CoV-2 clearance, increasing the risk of secondary infections. It is important to use the right treatment in the right selected patient.

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