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Causes and methods of preventing cytokine storm in immuno-oncology

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Abstract

Cytokine storm is an excessive immune response that can occur when using immunotherapy in oncology, especially in the case of the use of immune checkpoint inhibitors and other methods that enhance immune activity. The main causes of cytokine storm are hyperactivation of the immune system associated with excessive production of proinflammatory cytokines, which can lead to severe systemic inflammatory reactions and organ damage. Among the methods of preventing cytokine storm, careful selection and monitoring of therapy, the use of immunomodulators, as well as the development of biomarkers to predict the risk of its occurrence are distinguished. The use of combined therapeutic approaches, as well as monitoring the condition of patients and prompt response to early signs of an inflammatory reaction are key strategies in reducing the risk of developing a cytokine storm in immuno-oncology.

Keywords: Cytokine Storm; Immunooncology; Immune Control Points; Inhibitors; Inflammation; Immunomodulation; Therapeutic Strategies; Biomarkers.

1. Introduction

Immuno-oncology is one of the most promising fields in modern medicine, aiming to enhance the body's immune response against tumors. With the advent and development of immune checkpoint inhibitors and other immunomodulatory agents, immunotherapy has become a revolutionary method for treating various forms of cancer. However, alongside its high therapeutic potential, these approaches carry the risk of serious complications, one of which is cytokine storm.

The relevance of studying cytokine storms in immuno-oncology is driven by the increasing number of cases arising from the use of new immunotherapy methods, which specifically target and enhance the immune system's ability to attack tumors. Unlike other therapies, such as chemotherapy or radiation, immunotherapies rely on immune system activation, which increases the risk of excessive immune responses like cytokine storms. This makes understanding the causes of this complication and developing strategies to prevent it particularly critical in immuno-oncology, where immune modulation is both the key therapeutic mechanism and a potential source of life-threatening complications.

The aim of this work is to analyze the causes of cytokine storm in immuno-oncology and to evaluate current methods for its prevention.

1.1. Pathophysiology of Cytokine Storm in Immuno-Oncology

The cytokine storm, a potentially life-threatening immune response characterized by uncontrolled release of pro-inflammatory cytokines, has garnered significant attention in recent years. With the advent of new technologies and a deeper understanding of the immune system, researchers are continually striving to identify new biomarkers that can predict the onset of cytokine storms and pave the way for effective interventions.

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The systemic reaction associated with the release of large amounts of cytokines was first described in patients receiving monoclonal antibodies in preparation for kidney transplantation. J.H. Antin and J.L. Ferrara were the first to use the term "cytokine storm" [1] to describe the direct cytopathic effect of cytokines such as interleukin-1 and tumor necrosis factor-alpha in the context of graft-versus-host disease. Experimental studies have shown a significant increase in the mRNA levels of these cytokines under experimental conditions.

Sepsis associated with bacterial infections has also been considered in the context of excessive production of pro-inflammatory cytokines. Unlike the levels of bacterial components such as lipopolysaccharides, it was the levels of cytokines like interleukin-1, interleukin-6, and tumor necrosis factor-alpha that directly correlated with patient mortality. The administration of antibodies against tumor necrosis factor-alpha protected laboratory animals from septic shock and multiple organ failure, underscoring the importance of cytokine balance in the pathogenesis of sepsis.

The role of cytokine storm in the development of immunopathology during viral infections of the brain and internal organs has been extensively described, particularly concerning viral infections [1]. Among non-infectious causes, mechanical injuries, burns, pancreatitis, and other damages, as well as treatment with chemotherapeutic agents and monoclonal antibodies, are highlighted. Hypercytokinemia is also observed in patients with hereditary forms of hemophagocytic lymphohistiocytosis and rheumatic diseases.

The mechanisms supporting the development of a cytokine storm include the production and release of pro-inflammatory cytokines, which are normally absent from the bloodstream. Disruption of natural barriers, massive cell destruction, and imbalance between pro-inflammatory and anti-inflammatory cytokines can lead to uncontrolled increases in cytokine levels. In some cases, this is associated with genetic defects, such as abnormalities in perforin production, which lead to excessive macrophage activation and cytokine production. Other cell types, such as neutrophils and eosinophils, also play a significant role and can contribute to the inflammatory response [1].

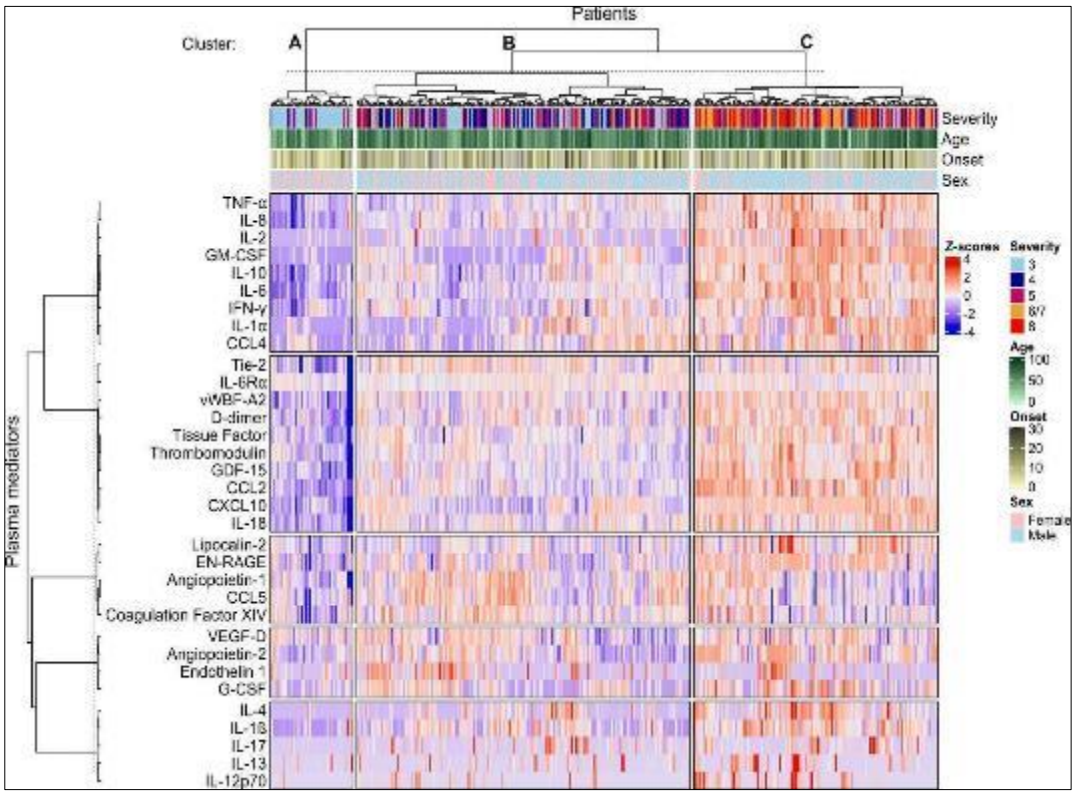

Figure 1 Clustered heat map of 33 immune mediators in plasma samples collected from patients hospitalized with COVID-19 at the time of inclusion in the study.

In immuno-oncology, the molecular mechanisms underlying cytokine storms include the activation of the NF-kB signaling pathway, leading to enhanced transcription of pro-inflammatory cytokine genes. The increased concentration of these cytokines in the blood triggers a cascade of inflammatory reactions, which can result in multiple organ failure, cytokine release syndrome (CRS), and acute respiratory distress syndrome (ARDS). Consequently, a cytokine storm can

have serious consequences for patients undergoing immuno-oncological therapy. Plasma mediators at the time of study inclusion demonstrated a broad, hypertrophied immune response in patients hospitalized with COVID-19 (Fig. 1).

Data on missing mediators were imputed, and values were scaled for each mediator. Rows and columns were clustered using K-means clustering.

The cytokine storm poses a particular threat in the context of COVID-19, where it can lead to immune deficiency, increasing the risk of secondary bacterial infections. Such uncontrolled inflammation can cause severe internal organ damage and even death, making the management of this process critically important in the treatment of severe viral infections [2].

The cytokine profile of patients with rheumatoid arthritis (RA) is characterized by increased production of interleukins-1 and -6 (IL-1 and IL-6) and tumor necrosis factor-α (TNF-α), leading to inflammation of the synovial membrane and destruction of cartilage and bone tissue. At the same time, there is inhibition of interleukins-4 and -10 (IL-4 and IL-10). The cytokine levels may vary depending on the disease phase, with elevated IL-6 and TNF-α being characteristic of the chronic course of RA. IL-1β, as one of the key mediators of inflammation in RA, stimulates the release of neutrophils, the growth and differentiation of lymphocytes, and participates in the initiation of the inflammatory process, ultimately leading to cartilage and bone destruction.

Studies [3] show that there is a correlation between cytokine levels, disease activity, joint deformity severity, and autoantibody levels in RA patients. For example, high levels of IL-6 and the chemokine IP-10 are observed in patients with high disease activity. Additionally, elevated concentrations of certain cytokines have been found to be associated with the development of joint erosions, confirming their significance in the pathogenesis of RA.

The pathophysiology of a cytokine storm involves several changes at the immune system level, such as elevated levels of various cytokines and their interaction with target cells. Studies conducted on COVID-19 patients have identified increased levels of cytokines such as interleukin-6, C-reactive protein, and ferritin, indicating the presence of a hyperinflammatory process. These markers can be used to assess disease severity and predict outcomes.

The cytokine storm triggered by SARS-CoV-2 can also lead to endothelial damage and other systemic complications, exacerbating the disease course and increasing the risk of fatal outcomes. The development of new therapeutic approaches aimed at suppressing the cytokine storm could be crucial in combating severe forms of COVID-19, especially in patients with comorbid chronic diseases and weakened immune systems [4].

1.2. Risk Factors and Clinical Manifestations of Cytokine Storm

A cytokine storm is a dangerous complication that can occur in severe forms of infectious diseases. This pathological process is characterized by excessive activation of the immune system, leading to a massive release of cytokines and the development of severe inflammation.

The main clinical signs indicating the onset of a cytokine storm include progressive deterioration of respiratory function, manifested by rapid breathing, difficulty inhaling, and the presence of wheezing. Additionally, inflammation of the lung tissue often develops, accompanied by shortness of breath and a dry cough. A typical symptom is a persistent fever, reaching febrile levels, which is resistant to standard antipyretic treatments. Furthermore, patients frequently experience dizziness, intense headaches, and confusion, which can progress to loss of consciousness. The skin may take on a bluish tint, indicating impaired oxygenation of tissues.

Patients may also report severe muscle and joint pain, as well as lower back pain that varies in intensity. General weakness, to the extent that the patient is unable to move independently, is another significant symptom.

The progression of respiratory disturbances can lead to the development of acute respiratory distress syndrome (ARDS), where oxygen therapy becomes vital. In the most severe cases, mechanical ventilation (MV) is required to maintain respiratory function.

A cytokine storm typically develops during the second week of illness, between days 8 and 14 after the first signs of viral infection appear. It is important for patients who have had COVID-19 to continue monitoring their condition closely, keeping track of blood pressure and pulse rate. If the above symptoms arise, it is crucial to seek immediate medical attention for further evaluation.

The diagnosis of a cytokine storm is based on a comprehensive analysis of data obtained through imaging methods, such as computed tomography (CT) of the lungs, and laboratory test results. CT scans can reveal characteristic ground-glass opacities in the lung tissue, indicating a severe inflammatory process. Laboratory tests may show a decrease in white blood cell count in the complete blood count, while biochemical analysis may reveal elevated levels of liver enzymes, creatinine, bilirubin, and other biomarkers indicative of organ dysfunction. Electrochemiluminescent blood assays help determine high concentrations of cytokines, confirming immune system hyperactivity.

In immuno-oncology, pathologies induced by a cytokine storm include acute respiratory distress syndrome (ARDS), multiple organ failure, and cytokine release syndrome (CRS), which arise from the excessive activation of the immune system triggered by immunotherapy, leading to the massive release of pro-inflammatory cytokines such as IL-6 and TNF-α. These conditions are characterized by pronounced inflammation, which can lead to life-threatening situations requiring urgent medical intervention and comprehensive treatment.

For this reason, timely diagnosis is crucial for the successful treatment of cytokine storms. The earlier appropriate treatment is initiated, the higher the chances of a favorable outcome and the lower the risk of fatal complications [5]. There are several pathologies with an elevated risk of life-threatening hypercytokinemia, as reflected in Table 1.

Table 1 A number of pathologies in which there is a risk of potentially life-threatening hypercytokinemia [6].

Pathology	Description
Viral Infections	One of the most dangerous clinical forms of hypercytokinemia occurs in severe infections, such as avian flu (H5N1), swine flu (H1N1). Specifically, the cytokine storm is considered a key factor contributing to fatalities in coronavirus infections accompanied by pneumonia and respiratory failure.
Sepsis and Septic Shock	A crucial aspect of the pathogenesis in these conditions is the sharp increase in cytokine levels, which is characteristic of generalized bacterial and fungal infections, such as staphylococcal and streptococcal infections.
Oncological Diseases	In the terminal stages of hematologic malignancies, such as leukemias and lymphomas, a cytokine storm may also be observed.
Graft Rejection	Hypercytokinemia can develop in the context of graft-versus-host reactions during hematopoietic stem cell or other organ transplants.
In Vitro Fertilization	In some cases, excessive activation of immune cells can lead to increased cytokine production, which is potentially dangerous for pregnant women undergoing embryo implantation procedures.

The primary mediators involved in the pathogenesis of a cytokine storm include tumor necrosis factor-alpha (TNF-α), gamma-interferon (IFN-γ), and interleukin-6 (IL-6). The interaction of these cytokines triggers cascade reactions that result in increased vascular permeability, cellular membrane damage, and disrupted microcirculation, which can ultimately lead to multiple organ failure.

The symptoms of a cytokine storm develop rapidly and include both nonspecific manifestations such as fever, headache, and myalgias, as well as more specific signs including respiratory failure and a sharp drop in blood pressure. In severe cases, acute respiratory distress syndrome (ARDS) develops, requiring immediate intensive care.

Complications of a cytokine storm can affect multiple organ systems. The most common complications include acute injuries to the lungs, kidneys, and liver, which can lead to multiple organ failure. In some cases, thrombosis and massive bleeding occur, significantly worsening the prognosis [6].

1.3. Methods of Preventing and Treating Cytokine Storm

The cytokine storm that occurs in COVID-19 represents a severe disruption in the functioning of the immune system, triggered by the SARS-CoV-2 virus. This results in an imbalance in the regulation of pro-inflammatory cytokine production, leading to their excessive production both locally and systemically. Consequently, a strong systemic inflammatory response is triggered, which can cause severe lung damage, including acute respiratory distress syndrome (ARDS). This condition is accompanied by hemodynamic disturbances and the development of multiple organ failure, significantly increasing the risk of a fatal outcome.

In this type of cytokine storm, there is a significant increase in the concentration of various interleukins in the blood serum, such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-12, as well as other pro-inflammatory factors, including granulocyte colony-stimulating factor, tumor necrosis factor-alpha (TNF-α), and interferons. IL-6, in particular, plays a key role in the pathological process by stimulating the differentiation of T- and B-lymphocytes and participating in the synthesis of acute-phase proteins. It also affects various cell types, including endothelial cells, contributing to their dysfunction and the development of endotheliopathy.

Endothelial dysfunction initiates two independent mechanisms: inflammatory and microthrombotic. The first mechanism amplifies the release of pro-inflammatory cytokines and exacerbates inflammation, while the second leads to platelet activation and the formation of excessive von Willebrand factor multimers, provoking microthrombosis and the development of disseminated intravascular coagulation (DIC) syndrome. This process is accompanied by thrombocytopenia and microangiopathic hemolytic anemia, resembling thrombotic thrombocytopenic purpura (TTP-like). The reduced activity of the enzyme ADAMTS 13, responsible for the cleavage of von Willebrand factor multimers, may be associated with systemic inflammation of infectious origin, contributing to coagulopathy and microcirculatory thromboses. Ultimately, this can lead to the development of ARDS with severe hypoxemia and multiple organ failure, which often results in death.

To diagnose the hyperimmune response in COVID-19, primary and additional criteria are identified. The primary criteria include the presence of fever with a temperature above 38°C and a C-reactive protein (CRP) level greater than 15 mg/L. Additional criteria include elevated lactate dehydrogenase (LDH) activity, ferritin levels above 400 ng/mL, elevated D-dimer levels, changes in the neutrophil-to-lymphocyte ratio, reduced hemoglobin and platelet levels, elevated triglyceride levels, interleukin-6, and aspartate aminotransferase (AST). A hyperimmune response is considered confirmed when one primary and one additional criterion are met.

The treatment of cytokine storm and macrophage activation syndrome involves the use of various medications. Depending on the clinical situation, glucocorticosteroids (such as dexamethasone or methylprednisolone), selective inhibitors of the Janus kinase family (such as baricitinib or tofacitinib), and genetically engineered biological agents, including IL-6 receptor blockers and IL-1 antagonists, may be used. The therapy is conducted strictly under medical supervision in a hospital setting [7].

In the spring of 2020, new information emerged indicating that the CD147 receptor, also known as basigin or extracellular matrix metalloproteinase inducer, may serve as an alternative pathway for SARS-CoV-2 to enter human cells. This receptor, belonging to the immunoglobulin superfamily, is present in human blood under normal physiological conditions. Moreover, it is known that similar mechanisms are used by other viruses, such as HIV-1 and the measles virus, as well as by malaria pathogens for their propagation.

Experimental data suggest that CD147 plays an important role in regulating systems such as the cardiovascular, nervous, and immune systems. Further research confirmed the hypothesis that CD147 serves as a receptor for SARS-CoV-2. An antibody, meplazumab, which specifically binds to this receptor, has shown the ability to significantly inhibit the virus's entry into host cells, as demonstrated by in vitro results. This points to the potential use of meplazumab in treating patients with severe forms of the disease.

Infection with SARS-CoV-2 triggers the development of a cytokine storm, characterized by uncontrolled release of inflammatory mediators and the activity of immune cells such as T-lymphocytes, macrophages, and NK cells. This process leads to tissue destruction and the spread of inflammation, causing systemic complications such as acute respiratory failure and respiratory distress syndrome.

The cytokine storm is accompanied by increased generation of reactive oxygen species, leading to oxidative stress and tissue hypoxia, which exacerbate damage to cellular structures, including mitochondria. This results in impaired cellular respiration and increased production of free radicals, further aggravating inflammation and lung damage, leading to severe respiratory complications [8]. The methods of preventing and subsequently treating cytokine storm are illustrated in Fig. 2.

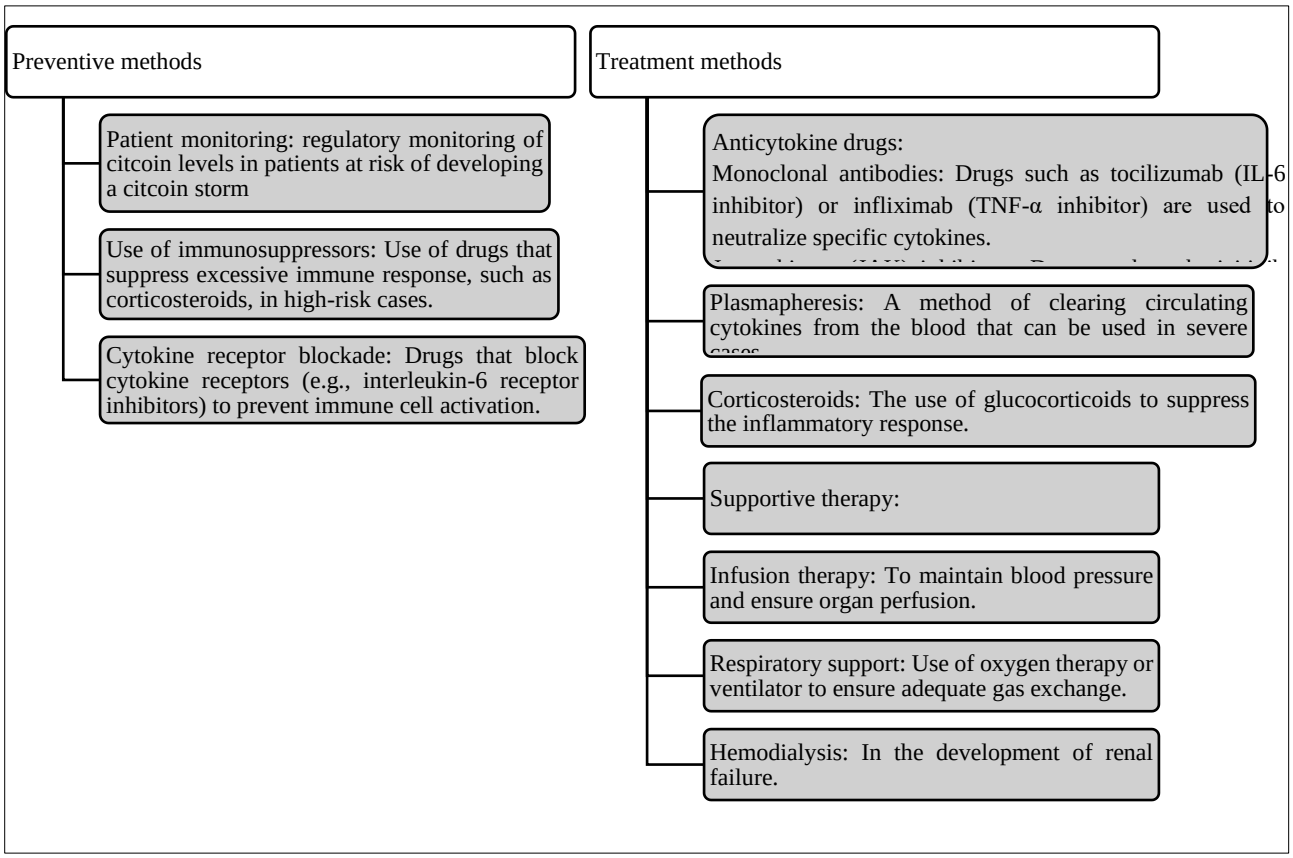

Figure 2 Methods of prevention and subsequent treatment of cytokine storm [8].

Thus, understanding the mechanisms of virus-cell receptor interactions and the consequences of this interaction for the immune system opens new opportunities for developing effective therapeutic strategies.

2. Conclusion

The cytokine storm in immuno-oncology represents a serious complication associated with the hyperactivation of the immune system and can lead to severe consequences for patients. A deep understanding of its mechanisms, as well as the development and application of strategies aimed at preventing and early detection of this condition, are critically important for the successful use of immunotherapy in oncology. Further research should focus on improving methods for predicting and controlling cytokine storms, which will enhance the effectiveness and safety of immunotherapy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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