

## The role of cytokine and its relation to depression and infection complications in pediatric cancer

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### Abstract

Inflammation plays a critical role in the progression of cancer in children. On the other hand, children with cancer experience abnormal activation of the inflammatory system. Moreover, it is known that these patients have a predisposition to depression. According to studies, moderate to severe depression was observed in about 63% of children with cancer and acute illness. Therefore, identifying inflammation-related biomarkers and targets in this regard is essential. The inflammation changes are related to cytokine deregulation, which in turn may influence the expression of depressive symptoms. Studies have reported that the deregulation of serum inflammatory cytokines, such as interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$  may influence depressive disorder in pediatric cancer patients. In addition, determining the risk of severe bacterial infection complications in pediatric cancer is essential to reduce the cost of therapy and hospitalization. However, the role of cytokines as an infection marker in these children is still a debate. Determining these plasma cytokine levels may have diagnostic value in assessing febrile neutropenia, although their crucial role in systemic inflammation is known. Given that evidence regarding the role of pro-inflammatory cytokine levels and relation to clinical parameters, including depression and infection in pediatric cancer patients is limited, we assessed the role of cytokine and its relation to depression and infection complications in pediatric cancer.

**Key words:** Cancer, Cytokine, Depression, Infection

### Introduction

Inflammation plays a main role in cancer progression.

Cancer-associated inflammation is characterized by a loss of normal growth regulation. This process is due to genetic and epigenetic changes in cancer-related regulatory genes (1). DNA methylation, histone modification, and microsatellite stability may be affected by inflammation (1). Cyclooxygenase 2 is an enzyme that metabolizes arachidonic acid to prostaglandins. It is expressed in inflamed tissues, affecting cell proliferation, aneuploidy, apoptosis, and angiogenesis. In addition, chronic inflammation leads to produce reactive oxygen species, and expression of chemokine and cytokine, including tumor necrosis factor (TNF), interleukin (IL)

1,6,12,13,17,22, and IL 23 which increase the risk of genomic instability, mutagenesis, and interactions between the local tumor microenvironment such as myofibroblasts and cancer stem cells (1-4).

### Cytokines

Cytokines are glycoproteins or polypeptides with a molecular weight of approximately under 30 KDa (4). Many cells release these soluble proteins, especially the innate and adaptive immune systems. They regulate processes, including inflammation, proliferation, differentiation, and the maturation of normal immunity. They affect approximately every biological process, including embryonic development and disease pathogenesis, alteration in

cognitive functions, specific response to antigen, the non-specific answer to infection as well as the progression of the degenerative processes of aging. The essential cytokines involved in inflammatory response induction are tumor necrosis factor (TNF)- $\alpha$ , IL-1, IL-6, and IL-8 (4). They in the immune system, as non-structural proteins, are the intercellular messengers and integrate the action of various cell types in different compartments into a coherent immune response (6). In addition, the function may be dependent on location and target cells (5, 6).

In addition, cytokines interact with cells through high-affinity receptors, often glycoproteins on the cell membrane, and are linked to intracellular second messenger signaling pathways. The interaction of cytokines may be through intracrine, autocrine and paracrine pathways (7).

#### ● Cytokine Networks

Tissue hemostasis is controlled by cascade and cytokine networks. In response to the stimulation of acute inflammation, the sequence of pro-inflammatory cytokines begins with the production of TNF- $\alpha$  and IL-1. They release IL-6, and subsequently hepatic acute-phase reaction (7). Simultaneously, the anti-inflammatory answers produce IL-1ra, IL-10, and soluble TNF receptors. It decreases the activity and the level of TNF- $\alpha$  and IL-1. Other cytokines, including transforming growth factor (TGF) and platelet-derived growth factor (PDGF), are produced and play the leading role in the tissue remodeling process (7).

#### ● Cytokines and malignancies

The importance of cytokines detection is due to their crucial signaling pathways. The concentration of cytokine is evaluated in many body fluids, cells, and tissues for prognostic and diagnostic purposes. Abnormal cytokine levels generate via various distinct mechanisms in cancer. The release of pro-inflammatory cytokines

happens as an answer to the tissue damage or cancer cells (7). Cytokines such as IL-4, IL-6, interferon-gamma (IFN- $\gamma$ ), soluble CD23 (sCD23), and soluble IL-2 receptors are mediators of immune response and inflammation.

The changes in the immune status of patients with different cancers may lead to the release of cytokines in circulation. Cytokines lead to promoting the growth and spread of cancers (7). Cancer cells can produce cytokines constitutively. These cytokines may have an autocrine effect on cancer cells or supporting tissues such as blood vessels and fibroblasts to create a suitable environment to growth of cancer. Moreover, these cytokines may induce normal cells, including endothelial cells and tumor-associated macrophages, to create additional cytokines that support the malignancy process (7). Studies have shown that the function of cytokines in malignancy is done via the following pathways.

- Uncontrolled Growth: Studies have demonstrated the role of growth factors, such as TGF $\alpha$ , in breast cancer. According the findings, 71% of ovarian cancer expressed the TNF gene.
- Angiogenesis and Stromal Formation: The formation of the new blood vessel is vital to the growth of tumor mass. Studies have shown a correlation between colon cancer cell proliferation and vascular endothelial growth factor.
- Metastatic Spread: Cytokines promote tumor cell adhesion in metastatic sites and activate local normal cells to cause tumor growth factors. IL-1 which is produced by tumor cells increases soluble intercellular adhesion molecules (7). Many cancers use cytokine to induce other cells to create growth factors.

## Cytokines and depressive symptoms in children with cancer

### • Depressive and pediatric cancer

Increased risk of depressive symptoms is seen in children with cancer at during and after therapy (8). The incidence and clinical characteristics of psychological manifestations in pediatric cancer have been considered in recent years (9-12). A report demonstrated moderate to severe depression in about 63% of children with cancer and acute illness (8).

Among these patients, severe depression was most common in those diagnosed with cancer (8).

Researchers have shown that depression score in the at-risk was higher in children with cancer than in children without cancer (13).

Not all patients with pediatric cancer develop depression, so this should be a multifactorial process (8). Psychosocial variables including social skills, gender, and self-worth play the leading role in the depressive symptoms of certain cancers in pediatric patients. Various variables such as environmental stressors, genetics, and trauma, malignancy, and cancer therapies may affect the level of inflammatory mediators, and contribute the development of depression (8).

### • Mechanism of inflammatory hypothesis and cytokine in depression

Abnormal activation of the inflammatory system is seen in children with cancer experience (8). Moreover, recent evidence have shown inflammation's role in depression (14-21). The identification of inflammation-related biomarkers and targets in this regard is essential. According to studies, cancer patients present an increased level of inflammatory cytokines, and almost half of these patients develop fatigue and depression (22-24).

Peripheral inflammatory cytokines affect the brain via various pathways. Circulating cytokines via access to the brain can

activate central nervous system inflammatory processes, causing the change of neurotransmitter networks (26-28). Mechanisms that explain this phenomenon includes the changes in the glutamate and monoamine, and the decrease in essential growth factors, including brain-derived neurotrophic element (29, 30).

Finally, these events lead to activating CNS immune cells such as microglia. In turn, activated microglia promotes inflammation which affects neurogenesis, neuroplasticity, and neurotransmitter metabolism leading to behavioral changes of depression (31). The inflammatory hypothesis of depression invokes inflammatory cytokines, neuronal excitotoxicity, and/or brain trophic factors, contributing the development of major depression (32).

### • Cytokine and depressive symptoms

Studies have shown the role of pro-inflammatory cytokines, including C-reactive protein (CRP), IL-6, IL-1b, and TNF- $\alpha$ , in patients who are diagnosed with major depressive disorder (32-36).

In addition, administering inflammatory stimulators, including direct inflammatory cytokines, endotoxin, and typhoid vaccine, to individuals without a history of depression leads to depressive symptoms (37, 38). Moreover, the change in cytokine levels and the function of the immune system are linked to suicidal symptomatology in patients with depression (39).

Another study assessed the role of cytokines in depression and demonstrated the elevation of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  in suicide victims and observed a potential link between the pathophysiology of suicidal behavior and inflammation related to cytokines (40). In addition, blocking cytokines such as TNF and the related cyclooxygenase 2 decrease the symptoms of depression in patients with cancer, hepatitis, and rheumatoid arthritis (41-44).

Therefore, biological mechanisms, including the change of cytokines and central nervous system response to inflammation, play a prominent role in the maintenance or induction of depression. It is assumed that inflammatory cytokine therapy may improve depression (43). Other studies demonstrated that Infliximab and Etanercept can improve the symptoms of depression and biomarkers of inflammation, including TNF- $\alpha$  and IL-6 in patients with depression (43, 44).

### **Cytokines and infection in pediatric cancer**

#### **• Pediatric cancer and infection**

Cancer children have capability to severe infections, particularly during chemotherapy. The first sign of bacterial infection is fever (4). Determining the risk of severe bacterial infection complications in pediatric cancer is essential to reduce the cost of therapy and hospitalization because 70 % of children with cancer have an increased risk of bacterial disease at first. In addition, 25% of them develop severe sepsis, and 3% of them die eventually. According to studies, febrile neutropenia is a serious and routine complication of cancer chemotherapy. Yet, no optimal antimicrobial regimen is identified for febrile neutropenia therapy. Children with febrile neutropenia receive a spectrum of antibiotics for treatment, although in most episodes, bacterial infection cannot be proven. Recent studies have shown the monotherapy use of piperacillin/tazobactam in children is popular (45, 46).

#### **• Cytokine and infection complication**

The role of cytokines as infection biomarkers is still debated (47). Regarding febrile neutropenia, IL-8 is one of the most prominently discussed cytokines that activate basophils, neutrophils, and T cells (47, 48). IL-8 with other biomarkers such as IL-6 and procalcitonin (PCT) are

considered reliable diagnostic biomarkers for bacteremia or sepsis (47, 49, 50), which can predict low-risk bacterial infections. But, IL-8 could not predict bacterial infections in children with febrile neutropenia (FN) (51, 52). MIP-1 $\alpha$  and MIP-1 $\beta$  activate macrophages, granulocytes, and monocytes and produce IL-1 $\alpha$ , TNF- $\alpha$ , and IL-6 (47). These cytokines are explained in the sepsis subject as predictors of the outcome but not in the subject of FN (53).

One study was conducted on children with febrile neutropenic and observed that Monocyte chemotactic protein (MCP) and CRP was significantly high in the first 24 hours of fever in bacteremic/septicemic patients (45).

TNF- $\alpha$  induces shock and fever, and its expression is dependent to the regulation of IL-10 and IL-6 (54). However, its role as a marker in febrile neutropenia could not be determined yet (55, 56). Karakurt et al. reported that the level of sIL-2R, CRP, PCT, IL-6, IL-8, and sTNFR2, are high in patients with fever >3 days; Still, they reported that the level of CRP, IL-6, IL-8, sTNFR2, and sIL-2R isn't as main predictors of serious infectious complication in children with cancer. These findings may help prevent the essential use of pro-inflammatory cytokines in routine clinical practice (45). Persson et al., demonstrated the effect of CRP, PCT, IL-6, and serum Amyloid A (SAA) on the clinical progress of febrile neutropenia (57). Another study reported that PCT and IL-6 levels are significantly high in complicated patients (fever > three days, clinically proven infections, and bacteremia), but CRP levels do not differ (45).

Another study reported that serum IL-2R increased in viral infection and post-transplant infections as well as tuberculosis (47). Fleischhack et al. also demonstrated increased serum sIL-2R levels during gram-negative bacteremia in pediatric cancer patients (58). Siegmond et al. assessed the regulation of cytokines

during febrile neutropenia in children with cancer. They found that cytokines including IL-8, MCP-1, and IL-1 $\beta$  increase during febrile neutropenia in the ex vivo sepsis model (47).

Another study reported that measuring IL-8 and IL-6 levels at the onset of febrile neutropenia could detect patient groups with low risk for bacteremia. According to the findings of this study, the determination of cytokine levels may have diagnostic value for assessing febrile neutropenia (4).

### **Molecular aspects of cytokine-based cancer Therapy**

The role of cytokines in cancer disease is important. The part of this interest is due to the use of cytokines to treat cancer. Following this, we will deal with this issue.

#### ● **Interleukin 2**

The use of cytokines for treating several diseases such as cancer began in 190 when the anticancer effect of IL-2 therapy was demonstrated. IL-2 was produced mainly by antigen-stimulated CD4<sup>+</sup> T-cells, CD8<sup>+</sup> T-cells, mast cells, and DCs, as well as NKT-cells. IL-2 is also effective in treating patients with melanoma in combination with anti-VEGF monoclonal antibody and dacarbazine monotherapy. The newest procedure in cancer immunotherapy is the combination of recombinant IL2 and immune checkpoint inhibitors for treating renal cells and melanoma. These combinations may improve to activate the immune system (59).

#### ● **Interleukin-12**

Interleukin 12 is a cytokine with an anti-tumor activity which is mostly mediated by stimulation of the production of IFN- $\gamma$  in cytotoxic cells and Th1 cells. IL-12 therapy increases CD56<sup>+</sup> NK cells and CD2 and LFA-1 expression, finally leading to increased cytotoxicity of IL12-treated NK cells (59).

#### ● **Interleukin 15**

Another cytokine that belongs to the family of IL2 is IL15 (60). IL12 and IL15 have overlapping functions. Mouse models demonstrated the efficacy of combining IL15/IL15R with an autologous vaccine against acute myeloid leukemia (61). But this research has not reached to clinical trial phase in humans. The combination of IL-15 with different therapeutic agents like immune checkpoint inhibitors should be actively investigated.

#### ● **Interleukin 21**

Interleukin 21 is considered a member of the IL2 family and one of the last cytokines discovered for clinical use in cancer therapy (59). One of the main functions of IL-21 is stimulating the proliferation of germinal center B cells (62) and induction the differentiation of CD40L-stimulated B cells in plasma cells. IL-21 can also activate NK cells via stimulating the expression of the natural cytotoxicity receptor NKp46 CD69 and enhancing cytotoxic activity. In addition, interleukin-21 activates and expands T-cell and NK cells (63). The combination of IL-21 with different mAbs, such as rituximab or sorafenib, is associated with antitumor activity (64).

#### ● **Interferon (IFN)**

Interferon is a group of cytokines that can be effective in cancer immunotherapy. IFNs are divided into three types based on the function and the target receptor (type I, type II ( $\gamma$ ), and type III ( $\lambda$ )) (65). IFN- $\alpha$ 2a is the cytokine for chronic myeloid leukemia therapy. IFN- $\gamma$  is another type II IFN cytokine which regulates the antitumor immune response and induces apoptosis of tumor cells (66).

### **Conclusion**

According to the findings of this study, children with cancer are faced with an increased risk of developing psychosocial and infectious challenges and experience abnormal activation of the inflammatory system. In addition, deregulation of serum inflammatory cytokines, including IL-1 $\beta$ ,

IL-6, and TNF- $\alpha$ , may be observed in children with depressive disorder. In addition, the role of cytokines as infection markers is still a debate, although their crucial role in systemic inflammation is known.

#### Conflicts of interest:

The authors declare that they have no competing interests.

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