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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)-1β, IL-6, and tumor necrosis factor (TNF)-α 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 meditation of normal immunity. They affect approximately every biological process, including embryonic development and disease pathogenesis, alteration in

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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)-α, 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-α 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-α 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-γ), 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 TGFa, 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.

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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- α, 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-1β, IL-6, and TNF-α 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).

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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-*α* 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-1α and MIP-1β activate macrophages, granulocytes, and monocytes and produce IL-1α, TNF-α, 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-α 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 sTNFRII, are high in patients with fever >3 days; Still, they reported that the level of CRP, IL-6, IL-8, sTNFRII, 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

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during febrile neutropenia in children with cancer. They found that cytokines including IL-8, MCP-1, and IL-1β 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+ T-cells, CD8+ 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-γ in cytotoxic cells and Th1 cells. IL-12 therapy increases CD56+ 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 cytokisnes 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 (γ), and type III (λ) (65). IFN-α2a is the cytokine for chronic myeloid leukemia therapy. IFN-γ 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-1β,

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IL-6, and TNF-α, 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.

References

1. Matary W, Bernstein Ch. Cancer Risk in Pediatric-Onset Inflammatory Bowel Disease. Front Pediatr 2020; 1-9.

2. Rubin DC, Shaker A, Levin MS. Chronic intestinal inflammation: inflammatory bowel disease and colitis-associated colon cancer. Front Immuno 2012; 8:107.

3. Francescone R, Hou V, Grivennikov SI. Cytokines, IBD, and colitis-associated cancer. Inflamm Bowel Dis2015; 21:409–18

4. Nijhuis C. Fever and neutropenia in cancer patients: the diagnostic role of cytokines in risk assessment strategies. Criti Rev Oncol/Hematol 2002; 44: 163–17

5. Decker M-L, Gotta V, Wellmann S , Ritz N. Cytokine profiling in healthy children shows association of age with cytokine concentrations. Sci Rep 2017; 7: 17842

6. Liu X., Fang, L., Guo T, Mei. Drug targets in the cytokine universe for autoimmune disease. Trends immunol34, 120–128

7. Dunlop R, FRACP . Cytokines and Advanced Cancer. Journal of Pain and Symptom Management 2000; 20: 214-232

8. Narendran G, Tomfohr L, Schulte F. Inflammatory cytokines and depression in children with cancer: A review of the literature. Pediatric Hematol Oncol 2018;1-9.

9. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 2013; 246:199–229**.**

10. Raison CL, MillerAH. Depression in cancer: newdevelopments regarding diagnosis and treatment.
Biol Psychiatry 2003; 54(3):283–294.

11. Li HC, Chung OK, Chiu SY. The impact of cancer on children's physical, emotional, and psychosocial well-being. Cancer Nurs 2010; 33(1):47–54.

12.. Bower JE, Ganz PA, Aziz N. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002; 64:604–611

13. Myers RM, Balsamo L, Lu X, et al. A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia. Cancer 2014; 120(9):1417–1425.

14. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative tomodern treatment target. Nat Rev Immunol 2016; 16(1):22–34.

15. Dunn AJ, Swiergiel AH, de Beaurepaire R. Cytokines asmediators of depression: what can we learn from animal studies? Neurosci Biohav Rev 2005; 29(4):891–909.

16. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the
pathophysiology of major depression. Biol Psychiatry 2009; 1; 65 (9):732–741.

17. Dowlati Y, Herrmann N, Swardfager W. A metaanalysis of cytokines in major depression.
Biol Psychiatry 2010; 67: 446–457.

18. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009; 71:171–186.

19. Harrison NA, Brydon L, Walker C. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry 2009; 66(5):407–414.

20. Reichenberg A, Yirmiya R, Schuld A. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry 2001; 58(5):445–452

[DOI: 10.18502/ijpho.v12i3.10063]

21. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 2007; 21(2):153–160.
22. Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr 2004; 32: 57–71.
23. Jehn CF, Kuehnhardt D, Bartholomae A. Biomarkers of depression in cancer patients. Cancer 2006; 107:2723–2729.
24. Musselman DL, Lawson DH, Gumnick JF. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med 2001; 344(13):961–966
25. DInarello A. Historical Review of Cytokines. Eur J Immunol 2007; 37(1): S34–S45
26.Pizarro TT, Cominelli F. Cloning IL-1 and the birth of a new era in cytokine biology. J Immunol 2007; 178:5411–5412
27.Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 2005; 23:479–490.
28. Leung BP, Xu D, Culshaw S, McInnes IB, Liew FY. A novel therapy of murine collagen-induced arthritis with soluble T1/ST2. J Immunol 2004; 173:145–150
29.Jin Y, Mailloux CM, Gowan K, Riccardi SL, LaBerge G, Bennett DC, Fain PR, Spritz RA. NALP1 in vitiligo-associated multiple autoimmune disease. N Engl J Med 2007; 356:1216–1225.
30. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet 2001; 29:301–305
31. Sforzini L, Antonietta Nettis M. Inflammation in cancer and depression: a starring role for the kynurenine pathway 2019; 1-9.
32. Li HC, Chung OK, Chiu SY. The impact of cancer on children's physical, emotional, and psychosocial well-being. Cancer Nurs 2010; 33(1):47–54.
33. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009; 65(9):732–741
34. Dowlati Y, Herrmann N, Swardfager W. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010; 67:446–457.
35. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009; 71:171–186.
36. Soegaard S, Rostgaard K, Skogstrand K. Neonatal Inflammatory Markers Are Associated with Childhood B-cell Precursor Acute Lymphoblastic Leukemia. Cancer Res 2018; 1-9.
37. Harrison NA, Brydon L, Walker C. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry 2009; 66(5):407–414.
38. Reichenberg A, Yirmiya R, Schuld A. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry. 2001; 58(5):445–452.
39. Gabbay V, Klein RG, Guttman LE. A preliminary study of cytokines in suicidal and nonsuicidal adolescents with major depression. J Child Adolesc Psychopharmacol 2009;19(4):423–430.
40. Pandey GN, Rizavi HS, Ren X. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. Psychiatry Res 2012; 4 6(1):57–63
41. Abbott R, Whear R, Nikolaou V. Tumour necrosis factor-α inhibitor therapy in chronic physical illness: A systematic review and meta-analysis of the effect on depression and anxiety. J Psychosom Res 2015; 79:175–184.
42. Köhler O, Benros ME, Nordentoft M. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials.

[DOI: 10.18502/ijpho.v12i3.10063]

JAMA psychiatry 2014; 71(12):1381–1391.
43. Raison CL, Rutherford RE, Woolwine BJ. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 2013; 70(1):31–41.
44. Tyring S, Gottlieb A, Papp K. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet North Am Ed 2006; 367(9504):29–33.
45. Karakurt D, Demirsoy U, Funda Corapcioglu F, Oncel S, Karadogan M, Sami Arisoy E. Do Proinflammatory Cytokine Levels Predict Serious Complication Risk of Infection in Pediatric Cancer Patients? Pediatric Hematol Oncol 2014; 31:415–424.
46. orapcıo˘glu F, Sarper N, Zengin E. Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatrıc cancer patients: a randomized comparison. Pediatr Hematol Oncol 2006; 23:177–186.
47. Siegmond A, Pagel J, Scholz T, Rupp J. Pro-inflammatory cytokine ratios determine the clinical course of febrile neutropenia in children receiving chemotherapy. Mol Cell pediatr 2020; 1-9.
48. Lanziotti VS, Póvoa P, Soares M, Silva JRLE, Barbosa AP, Salluh JIF. Use of biomarkers in pediatric sepsis: literature review. Rev Bras Ter Intensiva 2016; 28(4):472–482.
49. de Araujo OR, Salomão R, Brunialti MKC. Cytokine kinetics in febrile neutropenic children: insights on the usefulness as sepsis biomarkers, influence of Filgrastim, and behavior of the IL-23/IL-17 pathway. Mediat Inflamm 2017; 8291316-8291319.
50. Arif T, Phillips RS. Updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment and management of fever during neutropenia in children with cancer. Pediatr Blood Canc 2019;66(10):e2788-e2790.
51. Urbonas V, Eidukaitė A, Tamulienė I. The diagnostic value of interleukin-6 and interleukin-8 for early prediction of bacteremia and sepsis in children with febrile neutropenia and cancer. J Pediatr Hematol Oncol 2012; 34(2):122–127.
52.Hatzistilianou M, Rekliti A, Athanassiadou F, Catriu D. Procalcitonin as an early marker of bacterial infection in neutropenic febrile children with acute lymphoblastic leukemia. Inflam Res 2010; 59(5):339–347.
53. Chaudhry H, Zhou J, Zhong Y. Role of cytokines as a double-edged sword in sepsis. In Vivo 2013; 27(6):669–684.
54.Schulte W, Bernhagen J, Bucala R. Cytokines in sepsis: potent immunoregulators and potential therapeutic targets--an updated view. Mediat Inflamm 2013; 2013:165974
55.Buyukberber N, Buyukberber S, Sevinc A, Camci C. Cytokine concentrations are not predictive of bacteremia in febrile neutropenic patients. Med Oncol 2009; 26(1):55–61.
56. Tang Y, Liao C, Xu X. Evaluation of Th1/Th2 cytokines as a rapid diagnostic tool for severe infection in paediatric haematology/oncology patients by the use of cytometric bead array technology. Clin Microbiol Infect 2011; 17(11):1666–1673
57. Persson L, Engervall P, Magnuson A. Use of inflammatory markers for early detection of bacteraemia in patients with febrile neutropenia. Scand J Infect Dis 2004; 36: 365–371.
58.Fleischhack G, Kambeck I, Cipic D. Procalcitonin in paediatric cancer patient; its diagnostic relevance is superior to that of C reactive protein, interleukin 6, interleukin 8, soluble 2 receptor and soluble tumour necrosis factor receptor II. Br Haematol 2000; 111:1093–1102.
59. Daria S. Chulpanova, Kristina V. Kitaeva· Molecular Aspects and Future Perspectives of Cytokine-Based Anti-cancer Immunotherapy. Front Cell Dev Biol 2020; 1-9.

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60. Waldmann T. A. Cytokines in cancer immunotherapy. Cold Spring Harb. Perspect Biol 2018; 10:a028472-0248477.
61. Shi W, Dong L, Sun Q, Ding H, Meng J, Dai G. Follicular helper T cells promote the effector functions of CD8(+) T cells via the provision of IL-21, which is downregulated due to PD-1/PD-L1-mediated suppression in colorectal cancer. Exp Cell Res 2018; 372 35–42
62. Zotos D, Coquet J, Zhang Y, Light A. IL-21 regulates germinal center B cell differentiation and proliferation through a B cell-intrinsic mechanism. J Exp Med 2010; 207 365–378.
63. Chapuis A. G, Lee S M, Thompson J. A, Roberts I. M, Margolin K. A, Bhatia S, et al. Combined IL-21-primed polyclonal CTL plus CTLA4 blockade controls refractory metastatic melanoma in a patient. J Exp Med 2016; 213 1133–1139.
64. Timmerman J. M, Byrd J. C, Andorsky D. J, Yamada R. E, Kramer J. A phase I dose-finding trial of recombinant interleukin-21 and rituximab in relapsed and refractory low grade B-cell lymphoproliferative disorders. Clin Cancer Res 2012; 18 5752–5760.
65. Budhwani M, Mazzieri R, Dolcetti R. Plasticity of Type I interferon-mediated responses in cancer therapy: from anti-tumor immunity to resistance. Front Oncol 2018; 8:322.
66. Zaidi M. R. The interferon-gamma paradox in cancer. J Interferon Cytokine Res 2019; 39 30–38. 10.1089-1092.

[DOI: 10.18502/ijpho.v12i3.10063]