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Cytokine IL6, but not IL-1β, TNF-α and NF-κB is increased in paediatric cancer patients

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Cytokines are responsible for maintaining homeostasis as cell growth, differentiation, migration and apoptosis mediators. They play a pivotal role in immune responses to inflammatory reactions. In oncological diseases, the cross-talk between cells of the immunological system and cells of the tumour microenvironment is led by cytokines. Also, the overproduction of cytokines may change the tumour microenvironment and stimulate tumour development and growth. To test whether pro-inflammatory cytokines or associated with them transcription factor levels are changed in a group of 53 paediatric cancer patients, serum levels of IL-1β, IL-6, TNF-α and NF-κB were assessed and compared to measures in 25 healthy controls. Increased levels of IL-6 were found among patients in active oncological treatment (*P*=0.002) but not among patients whose treatment was completed. Our data suggest that IL6, but not IL-1β, TNF-α and NF-κB, is elevated as a result of the immune response in the microenvironment around the tumour and in blood cancers, among patients who were not infected at the time of blood collection. Thus, IL6 levels might serve as a potential biomarker of oncohematological diseases.

Keywords: cytokines, cancer, interleukins, biomarker, pediatric neoplasm

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Abbreviations: ATGL, adipose triglyceride lipase; BAFF, B-cell activating factor; CAFs, cancer-associated fibroblasts; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IL-1, interleukin 1; IL-1α, interleukin 1 α; IL-1β, interleukin 1β; IL-6, interleukin 6; TNF-α, tumour necrosis factor α; IL-8, interleukin 8; ILs, interleukins; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; NIK, NF-κB-inducing kinase; NK, natural killers; ROS, reactive oxygen species; TAMs, tumour associated macrophages; TME, tumour microenvironment; TRAF2/3, TNF receptor-associated factor 2/3; VEGF, vascular endothelial growth factor

INTRODUCTION

Cytokines are intercellular protein mediators which regulate many processes, including cell growth, differentiation, migration and apoptosis. They play a crucial role in immune responses to inflammatory reactions and, generally, are responsible for maintaining homeostasis. In the case of a healthy person, they are present locally in tissues or body fluids in relatively small amounts. High activity in low concentrations is a characteristic feature in certain pathological states.

These molecules are produced by many types of cells and may cause numerous reactions. Inversely, various groups of cytokines may play the same role. In addition, the source of cytokines may affect its final response, and even cause the opposite effect.

Cytokines create a complicated network of stimulation and inhibition processes (Jansen *et al*., 2022). Interleukins (ILs) were the first described growth and differentiation regulators expressed by leukocytes. With further studies, other factors were discovered in terms of cytokines, and it is now known that there are more than 50 interleukins and additional proteins (Brocker *et al*., 2010). Interleukins are divided according to their origin and functions, specifically to pro-inflammatory, proangiogenic, chemotactic or hematopoietic. Specific surface receptors are necessary for proper cytokine effect by increasing or decreasing its influence on cell metabolism.

The role of cytokines in malignant proliferation is widely studied. It is well known that the neoplastic process is associated with uncontrolled cell division and disturbances in metabolic regulation. Cancer cells are much better consumers of nutritional substances than normal tissue components due to their rapid growth. It includes amino acids, lipids, protein or glucose metabolism and its influence on the tumour microenvironment. The expression of adipose triglyceride lipase (ATGL) may be downregulated in some cancers and may be associated with glycolytic processes typical for most malignant tumours (Pan *et al*., 2013).

Moreover, tumour cells may adapt by metabolic reprogramming (Tang *et al*., 2021). Rapidly growing tumour mass requires new blood vessels, and angiogenesis takes place. But it is insufficient, and hypoxia is another process in this situation. Tumour cells use more likely energy from aerobic glycolysis and glutaminolysis or fatty acids, which is known as Warburg effect. Such a process may be connected with oncogene activation such as Myc, Ras, or inactivation of the p53 suppressor gene and some metabolic damage (Koppenol *et al*, 2011; Cairns *et al*., 2011). All these processes influence signal transmission and have an impact on immunometabolism in cancer. Cytokines play a role as mediators between cells of the immunological system and cells of the tumour microenvironment. Cancer cell – intrinsic and extrinsic signalling is needed for progression and invasion of the neoplastic process (Briukhovetska D *et al*., 2021).

Cytokines play different roles in uninhibited proliferation processes, such as paracrine and autocrine factors, proangiogenic agents, survival factors of neoplastic cells

and other elements that affect invasiveness and distant metastasis formation.

The role of the immune system, and thus the influence of cytokines in malignancies, cannot be overestimated. Inflammation, primarily chronic, and oxidative stress mediate different kinds of malignancies. Most of the studies on that correlation were collected from colon cancer patients who primarily have Crohn's disease (Monteleone *et al.*, 2012; Klampfer L, 2011; Borowczak *et al.*, 2022). Pro-inflammatory cytokines, such as IL-1β, IL-6 or TNF-α play a key role in proliferative diseases, and their overproduction may change the tumour microenvironment and stimulate tumour development. Also, activation of transcription factors such as NF-ϰB is involved in various cellular processes in neoplasms. This factor can inhibit apoptosis as well as enhance angiogenesis. Thus, it may play a role in developing both haematological neoplasms and solid tumours.

We have attempted to answer the question if changes in the level of the determined substances can serve as an early marker of neoplastic disease or be a prognostic marker of the outcome.

MATERIALS AND METHODS

Patients

Paediatric cancer patients, including patients with haematological malignancies and solid tumours, who were diagnosed and treated in the Department of Paediatrics, Haematology and Oncology, Medical University of Gdansk, Poland, were enrolled in the study. Twenty-five patients, between 1 and 18 years of age (mean age 8.04 years, median age six years), were during treatment, and twenty-eight patients, between 3 and 18 years of age (mean age 9.79 years, median age eleven years) were after treatment.

Inclusion criteria

We included children between 1 month and 18 years of age with confirmed neoplastic disease. The patients showed no signs of infection.

Control group

Twenty-five healthy children were recruited during routine medical checkup (14 males and 11 females), aged between 3 and 17 years (mean age 12.24 years, median age 14 years).

Laboratory analysis

Peripheral blood was collected from the patients during and after successful treatment; the average duration of treatment was about two years.

Measurements of IL-1β, IL-6 and TNF-α were assessed using R&D Systems Quantikine ELISA Kits (Minneapolis, MN, USA) and NF-ϰB using Nuclear Factor Kb P65 (NFKB P65), ELISA Kit (My BioSource, San Diego CA, USA). All assays were performed according to the procedure provided by the manufacturer. All analyses were performed in the laboratory of the Department of Clinical Nutrition Medical University of Gdansk, Poland.

Statistical analyses

The Wilcoxon rank-sum test was used to assess differences in subjects' age (years) and in levels of NF-ϰB (μmol/L), TNF-α (pg/mL), IL-6 (pg/mL) and IL-1ß (pg/mL) between patients before treatment, patients during treatment, patients after treatment and healthy controls. The distributions of NF-ϰB, TNF-α, IL-6 and IL-1ß were skewed as assessed by Kolmogorov-Smirnov test. Tests were two-tailed, and P-values ≤ 0.05 were considered statistically significant. Means and standard deviations, medians and 25th–75th percentiles were given for continuous variables. Statistical analyses were calculated using SAS 9.4 (NC, USA). XLStat (Addinsoft) programme was used to generate plots.

RESULTS

The study population consisted of 25 patients during treatment, 28 patients after treatment and 25 healthy controls (Table 1). Those groups did not differ significantly in age at the time of blood collection. A slightly

Table 1. Characteristics of study population.

		Patients during treatment	Patients after treatment	Healthy controls
*Age (years)	Mean, St Dev	8.04, 5.87	9.79, 4.63	12.24, 4.69
	(N)	(25)	(28)	(25)
	Median (q1-q3)	6 (3–14)	11 (6–12.5)	14 (9–16)
Sex	Females	8 (32%)	12 (42.86%)	11 (44%)
	Males	17 (68%)	16 (57.14%)	14 (56%)
Diagnosis	acute lymphoblastic leukemia	8 (32%)	3 (10.71%)	
	non-Hodgkin lymphoma	1 (4%)	1 (3.57%)	
	neuroblastoma	2 (8%)	14 (50%)	
	rhabdomyosarcoma	4 (16%)	2 (7.14%)	
	Wilms tumor	–	2 (7.14%)	
	retinoblastoma	–	1 (3.57%)	
	Hodgkin lymphoma	6 (24%)	5 (17.86%)	
	osteosarcoma	2 (8%)	–	
	Langerhans cell histiocytosis	2 (8%)	–	

*P=0.178 for a difference in age between patients during treatment *vs.* patients after treatment. *P=0.014 for a difference in age between patients during treatment *vs.* controls. *P=0.052 for a difference in age between patients after treatment vs controls

Table 2. Comparison of NF-κB, TNF-α, IL-6, IL-1 ß levels from patients before or after treatment and healthy controls.

		Patients during treatment	Patients after treatment	Healthy controls	*P**1	*P**2	*P**3
NF-κB	Mean, StDev	1.83, 1.66	2.57, 1.92	2.78, 2.91	0.092	0.273	0.618
(μmol/L)	(N)	(25)	(28)	(25)			
	Median (q1-q3)	1.42 (0.7-3.12)	1.71 (1.15-3.82)	1.45 (1.03-3.16)			
TNF-α	Mean, StDev	1.62, 1.45	1.32, 0.92	1.04, 0.64	0.624	0.109	0.154
(pg/mL)	(N)	(25)	(28)	(25)			
	Median (q1-q3)	1.38 (0.59-1.85)	0.98 (0.78-1.69)	0.90 (0.71-1.07)			
IL-6	Mean, StDev	6.34, 4.13	2.32, 2.55	2.75, 3.45	0.0002	0.002	0.563
(pg/mL)	(N)	(25)	(28)	(25)			
	Median (q1-q3)	6.16 (2.07-10.55)	1.27 (0.65-2.85)	1.19 (0.91-2.35)			
IL-1 ß #	Mean, StDev	0.1, 0.0709	0.10, 0.12	0.07, 0.06	0.203	0.116	0.950
(pg/mL)	(N)	(23)	(28)	(25)			
	Median (q1-q3)	0.09 (0.05-0.14)	0.05 (0.03-0.11)	0.06 (0.03-0.09)			

*Wilcoxon ranked-sum test; [1]patients during treatment *vs*. patients after treatment; [2]patients during treatment *vs*. controls; [3]patients after treatment *vs*. controls; # two outling values: 2.49, 6.08 pg/mL were removed from analyses

higher proportion of males were included in each group; males constituted 68% of patients, 57.14% of survivors and 56% of healthy subjects. More patients than survivors were diagnosed with acute lymphoblastic leukaemia (32% *vs*. 10.71%), while more survivors were diagnosed with neuroblastoma (50% *vs* 8%). Among survivors, two patients were diagnosed with Wilms tumour; one person was diagnosed with retinoblastoma. Among patients, two were diagnosed with osteosarcoma and two with Langerhans cell histiocytosis.

Levels of IL-1β, IL-6 or TNF-α and NF-κB were measured in blood samples collected from a healthy control group and pediatric oncological patients during treatment and post-treatment. Significantly higher levels of IL-6 were observed in the patients during active oncological treatment compared to both the control group and survivors (P=0.002, P=0.0002, respectively), as presented in Table 2, Figure 1. IL-6 levels in the post-treatment group were comparable to those in the control group (P=0.563). The mean value of IL-6 was 6.34±4.13 pg/mL among patients during active oncological treatment versus 2.75±3.45 pg/mL among healthy controls and 2.32±2.55 pg/mL among survivors.

In other parameters, such dependencies were not observed (Table 2, Fig. 1).

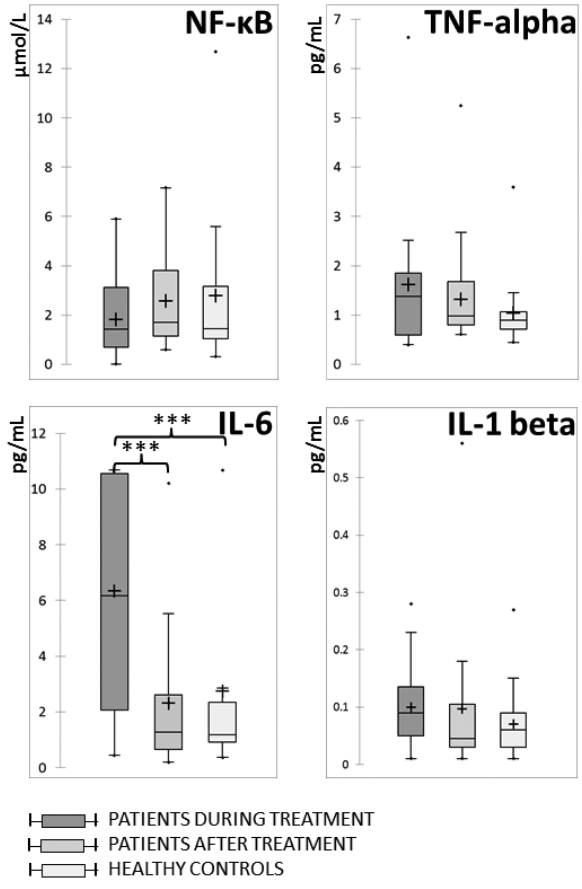

Figure 1. Levels of NF-κB, TNF-α, IL-6, IL-1β from patients before or after treatment and healthy controls.

DISCUSSION

Pediatric cancer patients constitute a particular group of patients, mainly due to the low incidence rate of this disease in children. Neoplasms type, both haematological and solid tumours, also differ from those in the adult population. Observations regarding the interleukin impact in children concern mainly IL-2 regarding its modulating effect on the immune system and the anti-tumour response promotion through lymphocyte activation and their differentiation in progressing or metastatic patients (Schwinger *et al*., 2005). It is well known that chronic inflammation concomitant with oxidative stress boosts tumour development, especially the skin, lung, colorectal or hepatocellular carcinoma (Bruni *et al*., 2020).

Pro-inflammatory cytokines such as IL-1β, IL-6 or TNF-α, which were under investigation in the present study, and NF-κB, are crucial for metabolic homeostasis. They are secreted by healthy cells, but their overproduction may lead to neoplastic transformation. Also, neoplastic cells derived from fibroblasts and macrophages also release IL-1, IL-6, TNF-α, that serve as source of paracrine factors (Bingle *et al*., 2002; Kunz-Schughart & Knuechel, 2002).

Among many cytokines present in pediatric oncology patients' sera, the ones determined by the authors seem to have a particular impact on the neoplastic process. The distinctive histology of childhood cancers makes it difficult to predict the behaviour of individual molecules, in contrast to the adult population where the inflammatory component of the neoplastic process has been relatively well studied (Dranoff, 2004; Greten *et al.* 2019; Mantovani *et al.*, 2019).

The tumour microenvironment (TME), which in addition to cancer cells, also contains cancer-associated fibroblasts (CAFs), pericytes, endothelial cells, and immune cells, plays a significant role in tumour proliferation and progression processes. Pro-inflammatory cytokines serve as mediators in these actions (Christofi *et al.*, 2019).

Our pediatric oncological patients showed significant differences in IL-6 levels during active treatment. Importantly, IL-6 values achieved those observed in the control group after the end of treatment. IL-6 is a multitasked substance. Its essential role is associated with the inflammatory response and active participation in the immunological processes. It may also be secreted by TME and cause further tumour development and progression (von Felbert *et al.*, 2005). Interleukin- 6 has a pro-oncogenic function as it may activate carcinogenesis. It is one of the mediators of cytokine release syndrome. IL-6 signals to cells through two opposite pathways. The classic pathway is anti-inflammatory and takes part in repair processes. The *trans*-signaling pathway promotes inflammation and may contribute to the progression of many diseases, including cancer (Kumari *et al.*, 2016). The classic pathway is based on transmembrane IL-6Rα receptors on a cell surface. The *trans* pathway occurs in the cells capable of expressing the gp130 protein.

IL-6 induces angiogenesis via the vascular endothelial growth factor. The elevated serum level of IL-6 in patients with colon and breast cancer or melanoma patients is a poor prognostic factor (Ma *et al.*, 2017; Kucera *et al.*, 2015). Furthermore, prostate cancer patients showed higher levels of this cytokine compared to a healthy control group. Moreover, it positively correlated with a higher Gleason score (Siemińska *et al.*, 2015). In metastatic prostate cancer patients, the serum level of IL-6 was higher than in patients with localized disease; hence it may serve as a prognostic factor (Michalaki *et al.*, 2004).

Similarly, in breast ductal carcinoma patients, Ma *et al.* (2017) demonstrated that elevated serum IL-6 levels positively correlated with more advanced disease stages and metastases to lymph nodes. Additionally, the authors noticed high levels of IL-6 in ER+ or HER2+ tumours in contrast to those with ER- or HER2 negative. In high-risk neuroblastoma pediatric patients, Egler and others (Egler *et al.*, 2021) showed increased IL-6 levels in their serum and bone marrow. The researchers analyzed the link between the levels of inter alia, IL-6 and the genetic polymorphism of this interleukin. Such results may suggest that particular interleukins could serve as potential cancer biomarkers.

Interleukin-1 was initially considered as a pro-inflammatory factor, which plays an essential role in severe systemic infections, but its part in the activation and stimulation of other cytokine secretion or prostaglandin production suggests that it should be considered in a broader aspect (Razavi *et al.*, 2015). It is also known that IL-1 may be partially involved in tumour promotion and could be responsible for metastasis. It develops via different mechanisms, such as matrix metalloproteinases expression, or affects the excretion of VEGF, IL-6, IL-8 or TNF-α by the surrounding tissues (Konishi *et al.*, 2005, Dinarello, 1996). Anti-inflammatory mechanisms are enhanced by interleukin-1 via the release of e.g., IL-6 (Mantovani *et al.*, 2019). Interleukin-1β belongs to the IL-1 family and is one of the structural components of IL-1. The other two are IL-1α and the IL-1 receptor antagonist. More importantly, IL-1β is initially produced by macrophages as a pro-protein and then converted into IL-1 ß with the use of caspase-1 (Teufel *et al.*, 2022). Both alarmins, IL-1β and IL-1α, may serve as promotors of carcinogenic mediators: nitric oxide and reactive oxygen species (ROS) (Mantovani *et al.*, 2019). Interleukin-1ß activates macrophages, suppresses NK function, and inhibits CD8+ lymphocytes by inducing neutrophils. The final effect is the production of pro-tumorigenic factors (Zhang *et al.*, 2020). Its role in cancer transformation and progression was observed in colon and prostate cancer patients, whose sera showed elevated levels of this factor (Hai *et al.*, 2016; Saylor *et al.*, 2012). Studies of human cancer cells from ovarian, breast, lung carcinoma, sarcoma and melanoma have shown that they are capable of producing or up-regulating Interleukin-1β (Elaraj *et al.*, 2006). Barrera and others (Barrera *et al.*, 2018) showed that elevated IL-1β serum concentrations in lung cancer patients positively correlated with a high percentage of myeloid-derived suppressor cells and were associated with worse prognosis and poor survival. Also, studies carried out on mice demonstrated an increased sera level of IL-1β and IL-6 following carcinogen administration (Narayan *et al.*, 2012). In our study, we did not observe increased values of IL-1β in our patients' sera, either during or after treatment, compared to the control group.

Another cytokine, tumour necrosis factor-α (TNF-α), also called cachexin, is of interest to those who study substances involved in developing various cancer types. It is mainly produced by macrophages (also TAMs- tumour associated macrophages) and monocytes, but also lymphocytes T, mast cells, fibroblasts and adipocytes. TNF-α is a part of the TNF superfamily, which also includes ligands and their receptors. When combined, most of them activate the nuclear transcription factor kappa (NF-ϰB) (Ware, 2008). Other signalling pathways for this factor are MAPK (mitogen-activated protein kinase) and the apoptosis signalling pathway. It is thought that cachexin may be both an anti-tumour and a pro-tumorigenic agent, depending on the dose (Dobrzycka *et al.*, 2009). There are reports of a direct effect on the stimulation of neoplastic transformation by inducing cell proliferation and transformation (Wang *et al*, 2008).

Increased TNF-α levels are related to a higher stage of cancer (Zhou *et al.*, 2014; Esquivel-Velazquez *et al.*, 2015). In metastatic prostate cancer patients who started hormonal therapy, elevated serum TNF-α levels are associated with a worse course of the disease and a worse prognosis (Sharma *et al.*, 2014). The researchers are not unanimous. Some authors showed lower serum TNF-α levels in colorectal cancer patients compared to the control group; others did not find it at all (Godos *et al.*, 2017; Abe Vincente *et al.*, 2014). It was found that high levels of this cytokine are associated with stage III and IV colorectal cancer (Obeed *et al.*, 2014). Additional studies focused on the association between TNF-α serum levels and the risk of colon cancer development or polymorphism of the gene encoding TNF-α *versus* cancer development risk. No correlation was found (Joshi *et al.*, 2014; Miao *et al.*, 2018). However, Ma and others (Ma *et al.*, 2017) indicated a correlation between serum concentrations of TNF-α, IL-6 and IL-8 and higher stages

of advancement (III-stage breast ductal carcinoma) and metastases to lymph nodes. We did not find any dependence for TNF-α in pediatric cancer patients compared to the control group, regardless of the treatment period.

Nuclear factor kappa B (NF-κB) constitutes a family of transcription factors which lead some important signaling pathways that might control cell differentiation, proliferation and angiogenesis during tumorigenesis (Taniguchi, 2018). The dysregulation of NF-κB is an essential contributor to the development of cancers and their progression or relapse. It is regarded as a potential therapeutic target for patients with neoplastic diseases. An NF-κB-inducing kinase (NIK), encoded by the gene *MAP3K14* is acclaimed as the central kinase controlling non-canonical NF-κB activation (Haselager, 2022). This NF-κB pathway is activated upon stimulation of the BAFF receptor, CD40, receptor activator of NF-κB or the lymphotoxin ß receptor. It accounts for the recruitment of TRAF2/3 to the receptor, resulting in the accumulation of NIK protein levels (Xiao *et al*., 2001). NIK plays a regulatory role in the process of inflammation. Loss of NIK is associated with severe immune defects, whereas NIK overexpression is observed in inflammatory diseases and malignancies. For this reason, targeting NIK and the non-canonical NF-κB pathway may display a therapeutic potential in various diseases (Fei *et al*., 2020; Jang *et al*., 2020). NFκB1 is a subunit of NF-κB. An aberrant activation of the latter is associated with cancer pathogenesis. The nuclear factor kappa B 1 (NFκB1, p105/p50) is a potential target gene of miR-497. It has been reported that NFκB1 plays various roles in the development and progression of cancers. On the other hand, NFκB1 may act as a tumour suppressor in some gastrointestinal cancers (hepatocellular carcinoma, gastric cancer) (Chen *et al*., 2022).

CONCLUSIONS

A significant increase in IL-6 in patients during oncological treatment and its absence after successful treatment may be helpful in monitoring the disease and may become an early biomarker of the neoplastic process in combination with other substances. The research carried out, and the results achieved indicate a certain important role of the tested substances in the process of oncogenesis and proliferation in oncohematological diseases in children. Further investigations are needed, including more potential biomarkers and patients with failure to check the course and level changes.

All the procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards – the study project of the study was approved by the Ethical Committee of the Medical University of Gdansk, Poland (NKBBN/868/2019).

Informed consent was obtained from the parents and patients over 16 years old.

Declaration

The authors declare that there are no conflicts of interest.

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