RESEARCH COMMUNICATION

Serum Levels of Interleukin-6 and Interleukin-10 in Turkish Patients with Aggressive Non-Hodgkin's Lymphoma

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Abstract

There exists strong evidence that tumor growth can be actively controlled by the host immune system and interleukins are known to play a significant role in immune response regulation. Inflammatory cytokines play important roles in the pathogenesis of lymphomas. This study was conducted to investigate the serum levels of IL-6 and IL-10 in patients with aggressive non-Hodgkin's lymphoma (A-NHL) and the relationships with prognostic parameters and therapy. These serum factors were measured in 46 A-NHL patients pathologically verified before and after chemotherapy in comparison with 21 healthy controls using enzyme-linked immunosorbent assays (ELISAs). There were significant differences in the serum IL-10 and IL-6 levels between A-NHL patients and controls (p=0,038 and p<0,001, respectively). None of the prognostic parameters analyzed was significantly correlated with the serum IL-6 concentrations. This was also true for serum IL-10 values, except for LDH and bone marrow involvement. Serum IL-10 levels were elevated in the group of patients with high level LDH compared with the group of patients with a normal level (p=0,017). Also, serum IL-10 levels were significantly different in the presence or absence of bone marrow involvement (p=0,016). In addition, we found a significant relationship between the serum levels of serum levels of IL-6 and IL-10 in patients with A-NHL (r=0,47, p<0,001). We found that serum IL-10 levels decreased due to chemotherapy effect independent of the chemotherapy response (p=0,027). However, serum IL-6 levels were not changed. In conclusion, our data suggest that higher serum IL-6 and IL-10 levels can be useful for diagnosis of A-NHL. However, our sample size is small, and larger scale research is needed in this field to provide new knowledge.

Key Words: Cytokines IL-6 and IL-10 - non-Hodgkin's lymphoma - Turkish patients

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Introduction

Diffuse large-cell lymphomas (DLBCLs) and other aggressive lymphomas are heterogeneous disease wich vary in biological expression and clinical course. Depending on risk factors, approximately 60–70% of patients achieve a complete response (CR) and the majority of these patients can expect to be cured with the use of doxorubucin-containing regimens (Armitage et al., 1988; Fisher et al., 1991). In contrast, patients not achieving a CR after first-line treatment have a poor long-term outcome (Cabanillas et al., 1998). Because of the curative intent of treatment and the dismal prognosis of patients who do not achieve complete remission or who have relapse, identification of risk groups is especially important. However, currently applied prognostic factors are, for the most part, clinical variables that reflect disease development but do not have a role in pathogenesis. Standart response criteria include clinical evaluations with imaging techniques that depend on changes in tumour size with limited prognostic value in the early course of treatment (Cheson et al., 2000).

Cytokines are intercellular short-acting soluble mediators that are involved in the pathogenesis of cancer (Suri et al., 1998). Some of them, e.g. IL-8, IL-6, and IN-1 stimulate angiogenesis and some of the others, e.g., IL-12 and IL-10 inhibit angiogenesis (Teicher et al., 1994). Cytokines play important roles in the pathogenesis of lymphomas. Serum concentration of the cytokines may be utilized as a marker of immunity status and prognosis and in cancer (Kozlowski et al., 2003).

The IL-6 family of cytokines performs fundamental functions in multiple biological processes, relevant to physiopathological conditions such as several autoimmune and inflammatory diseases (Alonzo et al., 1998; Boe et al., 1999). In addition, much evidence indicates a key role for IL-6 in lymphoproliferative conditions. B-cell lymphomas produce high levels of IL-6, wich in fact represents an important growt factor in at least some forms of this pathology. In addition, the presence of blasts in B-cell lymphoma patients has been shown to correlate with IL-6 production (Emilie et al.,

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1992). IL-6 is a potent lymphoid growth and differntiation cytokine that is produced by various types of cells, including bening and malignants B and T lymphocytes, monocytes, macrophages, fibroblasts, and hepatocytes (Van Snick, 1990; Heinrich et al., 1990). Its pleiotropic activities are reflected by its participation in the physiologic regulation of immune function, inflammatory responses, bone metabolism, and neural processes and by its effects on hematopoiesis (Kishimito et al., 1995). IL-6 has also been implicated in the pathogenesis of several lymphoproliferative disorders, including multiple myeloma, lymphoma, and Castleman disease (Ludwig et al., 1991; Yee et al., 1989), and it may be a prognostic factor for solid tumors, such as renal cell (Blay et al., 1992), epithelial ovarian (Berek et al., 1991) and prostate (Benihoud et al., 1999) cancers.

IL-10, also known as cytokine synthesis inhibitory factor, has multiple effects on lymphoid development. IL-10 exerts multiple biologic effects on hematopoitetic cell lineages, including monocytes, T and B lymphocytes (Rousset et al., 1992). It is a growtand differentiation factor for B cells in humans and growth factor for T lymphocytes in the Mouse model (MacNeil et al., 1990). Besides IL-10 exerts immunsuppressive properties: It inhibits antigen-specific T cell activation and blocks cytokine production by monocytes and macrophages in both human and mouse models (De Waal Malefyt et al., 1991).

In some studies, in patients with A-NHL, serum IL-6 and IL-10 levels were found to be high when compared with healthy individuals (Girardin et al, 1988; Tewari et al., 1990). Knowledge of the serum levels of these cytokines in patients with newly diagnosed A-NHL may help us to have some information about the possible prognosis, the activation of disease, and to decide on appropriate therapeutic approaches for individual patient. This study was conducted to investigate the serum levels of IL-6 and IL-10 before and after chemotherapy in patients with aggressive non-Hodgkin's lymphoma and the relationship with prognostic parameters.

Materials and Methods

Patients

During the period 2005 to 2007, 46 patients with the diagnosis of A-NHL admitted to the Institute of Oncology, Istanbul, Turkey, were included in our study. Forty-six patients are listed in Table 1. A number of clinical pathological parameters were shown including on age, tumor stage, tumor histology, B-symptoms, extranodal lesion, performance status, bone marrow invasion, serum LDH and γ2-microglobulin levels. The clinical characteristics of patients are summarized in Table 1. Histopathological diagnosis were in accordance with the WHO classification system (Jaffe et al., 2001). The study population consisted of patients with newly diagnosed aggressive lymphoma defined as DLBCL and follicular lymhoma grade III. Because of the fact that low-grade lymphomas in the view of clinical and treatment approaches, there were not included in the study.Inıtial staging according to the Ann Arbor system was performed at diagnosis before initiation of treatment. Staging procedures included computed tomography (CT) scan of the chest, abdomed and pelvis and unilateral bone marrow biopsy. Serum samples were obtained on admission and after completion of chemoterapy. All patients were treated with cyclophosphamide, doxorubicin, vincristin and prednizone (CHOP) with 3-week intervals. None of the patients had received previous therapy including immunomodulators, cytokines or steroids.

Table 1. Patient Characteristics

Parameter		n	%
Sex	Man	28	60.0
	Woman	18	40.0
Age (median,range)		52	(21–82)
	≤ 60	34	
	>60	12	
Histology	Diffuse large cell	40	86.9
	Follicular grade 3	6	13.1
Stage	I	15	32.6
	II	15	32.6
	III	7	15.3
	IV	9	19.5
Response rate	Complete	39	84.7
	Partial	7	15.3
B-symptoms	Absent	27	58.6
	Present	19	41.4
Performance status	0	24	52.2
	1	14	30.4
	2	8	17.4
Bone marrow	Positive	2	4.3
	Negative	44	95.7
Extra nodal lesion	Yes	17	37.0
	No	29	63.0
Serum LDH level	≤ 1x normal	23	50.0
	> 1x normal	23	50.0
Serum β2 globulin	≤ 1x normal	13	28.3
	> 1x normal	6	13.0
	Missing	27	58.7

Further exclusion criteria were to be pregnant, severe infections, known allergic disease and poor performance status. Written informed consent was obtained from all patients before study. Normal controls (n=20) were recruited from among the institute personel, and all were in excellent health at the time of the study.

Measurement of IL-6 AND IL-10 Levels

Circulating IL-6 and IL-10 levels were evaluated by solid-phase enzyme-linked immunosorbent assay (Biosource International, Inc. California, USA) using 96-well microplates in accordance with the manufacturer's instructions.

A monoclonal antibody specific for IL-6 has been coated onto the wells of the microtiter strips provided. Samples, including standards of known IL-6 content, control specimens, and unknowns, are pipetted into these wells, followed by the addition of a biotinylated monoclonal second antibody. During the first incubation, the IL-6 antigen binds simultaneously to the immobilized (capture) antibody on one site, and to the solution phase biotinylated antibody on a second site. After removal of excess second antibody, Streptavidin-Peroxidase (enzyme) is added. This binds to the biotinylated antibody to

complete the four-member sandwich. After a second incubation and washing to remove all the unbound enzyme, a substrate solution is added, which is acted upon by the bound enzyme to produce color. The color development is stopped with the stop solution and the intensity of the color was measured at 450 nm using ELISA reader (Rayto RT-1904C Electronics Inc.China). A monoclonal antibody specific for Hu IL-10 has been coated onto the wells of the microtiter strips provided. Samples, including standards of known Hu IL-10 content, control specimens, and unknowns, are pipetted into these wells. During the first incubation, the Hu IL-10 antigen binds to the immobilized (capture) antibody on one site. After washing, a biotinylated monoclonal antibody specific for Hu IL-10 is added. During the second incubation, this antibody binds to the immobilized Hu IL-10 captured during the first incubation. After removal of excess second antibody, Streptavidin-Peroxidase (enzyme) is added. This binds to the biotinylated antibody to complete the four-member sandwich. After a third incubation and washing to remove all the unbound enzyme, a substrate solution is added, which is acted upon by the bound enzyme to produce color. The color development is stopped with the stop solution and the absorbance of each well is measured at 450 nm using a microtiter plate reader (Rayto RT-1904C Electronics Inc.China).IL-6 and IL-10 levels were expressed as picogram per mililiter (pg/mL).

Table 2. Distribution of Serum IL-10 and IL-6 Values in Non-Hodgkin's Lymphoma and Healthy Controls

	Patients (n=46)	Controls (n= 20)	p
IL-10	13.0 (6.8 - 638.9)	11.3 (8.0 - 13.5)	0.038
IL-6	14.1 (37.5 - 203.7)	6.0 (2.8 - 12.3)	0.001

Table 3. Distribution of Serum IL-10 and IL-6 Values in Patients with Non-Hodgkin' s Lymphoma as a Function of Different Variables

Parameter		IL-10	IL-6
Age	(≤60 vs >60)	ns	ns
Sex	(Man vs Woman)	ns	ns
Histology	(Diffuse large cell vs others)	ns	ns
Stage	(I,2 vs 3,4)	ns	ns
Performance status	(0,1 vs 2)	ns	ns
Response Rate	(Complete vs partial)	ns	ns
B-symptoms	(Absent vs Present)	ns	ns
LDH	(≤ 1x normal vs > 1x normal)	0.017	ns
Serum β2 microglobulin level	(≤ 1x normal vs > 1x normal)	ns	ns
Bone marrow involvement	(Yes vs No)	0.016	ns
Extra nodal lesion	(Yes vs No)	ns	ns
Progression	(Absent vs Present)	ns	ns

ns, not significant

Table 4. Distribution of Serum IL-10 and IL-6 Values in Patients with Non-Hodgkin' s Lymphoma Before and After Chemotherapy

	Before	After	p
IL-10	13.0 (6.8 - 638.9)	10.6 (7.1 - 165)	0.027
IL-6	14.1 (37.5 - 203.7)	8.0 (3.1 - 80.4)	0.19

Statistical Analysis

Data analyses were performed using SPSS soft-ware (SPSS–16, Chicago, IL, USA). The Wilcoxon signed ranks test was used for statistical significance. Correlation was calculated with Spearman's correlation test, p values of < 0,05 were considered to be significant.

Results

Table 2 shows higher IL-10 and IL-6 levels in A-NHL patients than controls. There was a significant difference in the serum IL–10 and IL–6 levels between non-Hodgkin's lymphoma patient and controlgroups (p=0.038 and p<0.001, respectively). Table 3 shows the correlation between serum IL–10 and IL–6 levels and clinicopathological factors. None of the prognostic parameters analyzed was significantly correlated with the serum IL-6 concentrations. This was also true for serum IL-10 values, except for LDH and bone marrow involvement. Serum IL-10 levels were elevated in the group of patients with high-level LDH compared with the group of patients with a normal level of LDH (p=0.017). Also, serum IL-10 levels were significantly different in the presence or absence of bone marrow involvement (p=0.016). In addition, we found a significant relationship between the serum levels of IL–10 and IL–6 in patients with A-NHL (r=0.47; p<0.001).

When we analyzed the effect of chemotherapy on serum parameters, we found that serum IL–10 levels were decreased due to chemotherapy effect independently from chemotherapy response (p=0.027). However, serum IL-6 levels were not changed by chemotherapy (p=0.19) (Table 4).

Discussion

There exists strong evidence that tumor growth can be actively controlled by the host immune system and interleukins are known to play a significant role in immune response regulation (Urosevic et al., 2003). Inflammatory cytokines play important roles in the pathogenesis of lymphomas and may reflect underlying biological processes including tumour-host interactions with prognostic information that is not afforded by conventional clinical parameters.

The IL–6 family of cytokines performs fundamental functions in multiple biological processes, relevant to physiopathologycal conditions such as several autoimmune and inflammatory disease (Alonzi et al., 1998; Boe et al., 1999). In addition, much evidence indicates a key role for IL-6 in lymphoproliferative conditions. Serum levels of IL-6 were previously found to be elevated in both relapsed and newly diagnosed cases of hodgkin and non-hodgkin lymphoma (Kurzrock et al., 1993; Seymour et al., 1997), and IL-6 has been implicated in the pathogenesis of several lymphoid disorders (Ludwig et al., 1991; Klein et al., 1995). Large quantities of IL-6 are produced by the germinal centers of hyperplastic lymph nodes from patients with Castleman's disease and have been implicated in the clinical manifestations of this syndrome (Yoshizaki et al., 1989). Culture supernatants

of neoplastic cells from a patient with advanced Ki-1-positive lymphoma associated with fever and bone destruction have been shown to produce high levels of IL-6 (Agematsu et al., 1991) and expression of both IL-6 and IL-6 receptors has been demonstrated in Hodgkin's disease (Pluda et al., 1993). Furthermore, an autocrine role for IL-6 in two lymphoma cell lines has been suggested by Yee et al. and this molecule may act as a growth factor for a Lennert's lymphoma derived T-cell line (Yee et al., 1989). In particular, IL-6 has been shown to be a growt factor for multiple myeloma cells. It has been suggested that circulating IL-6 levels are an important prognostic factor for multiple myeloma (Ludwig et al., 1991) and for renal cell carcinoma (Blay et al., 1992). Recently, IL-6 has been targeted for its role in susceptibility to psoriasis and rheumatoid arthritis (Naka et al., 2002).

B lymphoma cell lines, EBV-transformed B cells, activated T cells, and macrophages have the capacity to produce IL-10 in vitro in humans (Suda T et al, 1990; Lauta, 2001). IL-10 also known as cytokine synthesis inhibitory factor, has multiple effects on lymphoid development. Detectable IL-10 was found in all histologic or immunologic subtypes of NHL; a result that would lead to the conclusion that follicular and germinal B lymphocytes as well as T lymphocytes at different stages of differentiation are able to produce IL-10 after transformation. Alternatively, IL-10 may be produced by normal cells under deregulated stimulation by malignant cells (Burdin et al., 1993). The high concentrations of IL-10 found in patients with NHL and possibly present in tumor sites could concervably exert an inhibitory effect on macrophage and antigen-specific T cell response at the tumor site and thus contribute to lymphoma progression in vivo (Benjamin et al., 1992).

In this study, we found significantly elevated serum levels of IL-6 and IL-10 in patients with A-NHL. In aggrement with our study, El-Far et al (El-Far M et al, 2004) reported significant difference in serum of IL-6 and IL-10 levels of patients compared with healthy control group.

A second objective of our study was to investigate the relationship between prognostic factors and serum IL-6 and IL-10 levels. In our study, none of the prognostic parameters analyzed was significantly correlated with serum IL-6 levels. However, we determined a statistically significant reletionship between serum IL-10 levels and high LDH levels and bone marrow involvement.

High IL-6 levels were significantly correlated with several other established clinical and laboratory adverse features, such as B symptoms, elevated serum levels B2-microglobulin or LDH, bulky disease, poor performance status, advanced Ann Arbor stage, age older than 60 years, and an unfavourable International Prognostic Index Score (is the most widely accepted prognostic factor model for patients with A-NHL). Also, age, stage, LDH level, performance status and number of extranodal involvement in aggressive lymphomas were introduced as IPI by Shipp et al (Shipp et al., 1993). These criteria are used for treatment plans and determination of the prognosis in patients with aggressive lymphomas. In the literature, there are several studies that confirm the fact that the serum levels of cytokines might also be some important prognostic factors in aggressive lymphomas. Fabre-Guillevin et al found a relation with IL-6 both with prognosis and prognostic index but not for IL-10 in 116 patients with aggressive lymphomas (Fabre-Guillevin et al., 2006). Kurzrock et al suggest a srong correlation between serum IL-6 levels and the presence of B symptoms (Kurzrock et al., 1993). In the study of Serebriakov et al, the marked relationship was found between the IL-6 levels and the stage of the disease (Serebriakov et al., 1998). Stasi et al reported that there was no correlation between clinicohematologic parameters and IL-10 levels (Stasi et al., 1994). Our results are similar, we found no significant differance in the serum IL-6 levels and prognostic parameters. However, we determined a statistically significant relationship between elevated IL-10 levels and high serum LDH levels. In contrary to our study, Blay et al. reported that serum IL-10 levels was not correlated to serum LDH (Blay et al., 1992). Further, we found significant correlation between IL-10 levels and bone marrow involvement. Neither does any other study exist in the literature. To our knowledge, this is the first report on serum IL-10 levels which shown the relation between high serum levels and bone marrow involvement in A-NHL patients.

Potential changes in the serum levels of cytokines after chemotherapy were investigated. In the study of Pedersen et al (2005), a significant decrease of IL-6 was observed in the first weeks after CHOP therapy in patients achieving a complete remission, comparable with its level before the initiation of treatment. Similarly, Seymour et al (1997) reported that IL-6 levels return to normal in patients with Hodgkin lymphoma who achieve complete response after treatment. Stasi et al (1994) reported that IL-6 levels progressively declined to normal ranges in responding patients, whereas they remained elevated in responders . In the present study, we found no change in the serum levels of IL-6 after CHOP therapy. Thus, our results are not in aggrement with the literature. The other finding in the present study is the serum level reduction of IL-10 which occurs with chemotherapy. Application of chemotherapy provided significant decrease in serum levels of IL-10 independently from chemotherapy response. To our knowledge, this is the first study in which serum IL-10 levels decreased after chemotherapy. In contrast, Cortes et al (1995) found no correlation between IL-10 levels and achievement of complete remission.

In conclusion, the present study showed higher serum IL-6 and IL-10 levels in A-NHL patients compared with healthy controls. Therefore, it seems that those circulating factors also might have a diagnostic utility in diagnosis of A-NHL. However, our sample size is small, and larger scale research is needed in this field, and exciting new knowledge will ultimately emerge. In addition, considering the critical role that cytokines play in the differentiation and/or proliferation of normal and neoplastic B-cells, further investigation of the biological impact of high levels of those cytokines on the pathogenesis or progression of lymphomas is clearly warranted.

References

Agematsu K, Takeuchi S, Ichikawa M, et al (1991). Spontaneous production of interleukin-6 by Ki-1-positive large-cell anaplastic lymphoma with extensive bone destruction. *Blood*, **77**, 2299-301.

Alonzi T, Fattori E, Lazzaro D, et al (1998). Interleukin 6 is required for the development of collagen-induced arthritis. *J Exp Med*, **187**, 461-8.

Armitage JO, Cheson BD (1988). Interpretation of clinical trials in diffuse large-cell lymphoma. *J Clin Oncol*, **6**, 1335-47.

Benihoud K, Yeh P, Perricaudet M (1999). Adenovirus vectors for gene delivery. *Curr Opin Biotechnol*, **10**, 440-7.

Benjamin D, Knobloch TJ, Dayton MA (1992). Human B-cell interleukin-10: B-cell lines derived from patients with acquired immunodeficiency syndrome and Burkitt's lymphoma constitutively secrete large quantities of interleukin-10. *Blood*, **80**, 1289-98.

Berek JS, Chung C, Kaldi K, et al (1991). Serum interleukin-6 levels correlate with disease status in patients with epithelial ovarian cancer. *Am J Obstet Gynecol*, **164**, 1038-42.

Blay JY, Negrier S, Combaret V, et al (1992). Serum level of interleukin 6 as a prognosis factor in metastatic renal cell carcinoma. *Cancer Res*, **52**, 3317-22.

Boe A, Baiocchi M, Carbonatto M, Papoian R, Serlupi-Crescenzi O (1999). Interleukin 6 knock-out mice are resistant to antigen-induced experimental arthritis. *Cytokine*, **11**, 1057-64.

Burdin N, Péronne C, Banchereau J, Rousset F (1993). Epstein-Barr virus transformation induces B lymphocytes to produce human interleukin 10. *J Exp Med*, **177**, 295-304.

Cabanillas F, Velasquez WS, McLaughlin P, et al (1988). Results of recent salvage chemotherapy regimens for lymphoma and Hodgkin's disease. *Semin Hematol*, **25**, 47-50.

Cavalli F (1991). Treatment of lymphomas. *Bailleres Clin Haematol*, **4**, 157-79

Cheson BD, Horning SJ, Coiffier B, et al (2000). Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*, **18**, 2351.

Cortes JE, Talpaz M, Cabanillas F, Seymour JF, Kurzrock R (1995). Serum levels of interleukin-10 in patients with diffuse large cell lymphoma: lack of correlation with prognosis. *Blood*, **85**, 2516-20.

De Waal Malefyt R, Abrams J, Bennett B, Figdor CG, De Vries JE (1991). Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. *J Exp Med*, **174**, 1209-20.

El-Far M, Fouda M, Yahya R, El-Baz H (2004). Serum IL-10 and IL-6 levels at diagnosis as independent predictors of outcome in non-Hodgkin's lymphoma. *J Physiol Biochem*, **60**, 253-8.

Emilie D, Coumbaras J, Raphael M, et al (1992). Interleukin-6 production in high-grade B lymphomas: correlation with the presence of malignant immunoblasts in acquired immunodeficiency syndrome and in human immunodeficiency virus-seronegative patients. *Blood*, **80**, 498-504.

Fabre-Guillevin E, Tabrizi R, Coulon V, et al (2006). Aggressive non-Hodgkin's Lymphoma: concomitan evaluation of nterleukin-2, soluble interleukin-2 receptor, interleukin-4, interleukin-6, interleukin-10 and correlation with outcome. *Leuk Lymphoma*, **47**, 570-2.

Fisher RI, Gaynor ER, Dahlberg S, et al (1991). Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced Non-Hodgkin's Lymphoma. *N Engl J Med*, **328**, 1002-6.

Gause A, Scholz R, Klein S, et al (1991). Increased levels of circulating interleukin-6 in patients with Hodgkin's disease. *Hematol Oncol*, **9**, 307-13

Girardin E, Grau GE, Dayer JM, Roux-Lombard P, Lambert PH (1988). Tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. *N Engl J Med*, **319**, 397-400.

Heinrich PC, Castell JV, Andus T (1990). Interleukin-6 and the acute phase response. *Biochem J*, **265**, 621-36.

Jaffe ES, Haris NL, Vardiman JW, Stein H (2001). Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumours, Lyon: IARC Press.

Kishimoto T, Akira S, Narazaki M, Taga T (1995). Interleukin-6 family of cytokines and gp130. *Blood*, **86**, 1243-54.

Klein B, Zhang XG, Lu ZY, Bataille R (1995). Interleukin-6 in human multiple myeloma. *Blood*, **85**, 863-72.

Koz_owski L, Zakrzewska I, Tokajuk P, Wojtukiewicz MZ (2003). Concentration of interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) in blood serum of breast cancer patients. *Rocz Akad Med Bialymst*, **48**, 82-4.

Kurzrock R, Redman J, Caballinas F, et al (1993). Serum interleukin-6 levels are elevated in lymphoma patients and correlate with survival in advanced Hodgkin's disease and with B symptoms. *Cancer Res*, **53**, 2118-22.

Lauta VM (2001). Interleukin-6 and the network of several cytokines in multiple myeloma: an overview of clinical and experimental data. *Cytokine*, **16**, 79-86.

Ludwig H, Nachbaur DM, Fritz E, Krainer M, Huber H (1991). Interleukin-6 is a prognostic factor in multiple myeloma. *Blood*, **77**, 2794-5.

MacNeil IA, Suda T, Moore KW, Mosmann TR, Zlotnik A (1990). IL-10, a novel growth cofactor for mature and immature T cells. *J Immunol*, **145**, 4167-73.

Naka T, Nishimoto N, Kishimoto T (2002). The paradigm of IL-6: from basic science to medicine. *Arthritis Res*, **3**, 233-42.

O'Garra A, Stapleton G, Dhar V, et al (1990). Production of cytokines by mouse B cells: B lymphomas and normal B cells produce interleukin 10. *Int Immunol*, **2**, 821-32

Pedersen LM, Klausen TW, Davidsen UH, Johnsen HE (2005). Early changes in serum IL-6 and VEGF levels predict clinical outcome following first-line therapy in aggressive non-Hodgkin's lymphoma. *Ann Hematol*, **84**, 510-16.

Pluda JM, Venzon DJ, Tosato G, et al (1993). Parameters affecting the development of non-Hodgkin's lymphoma in patients with severe human immunodeficiency virus infection receiving antiretroviral therapy. *J Clin Oncol*, **11**, 1099-107.

Rousset F, Garcia E, Defrance T, et al (1992). Interleukin-10 is a potent growth and differentiation factor for activated human B lymphocytes. *Proc Natl Acad Sci USA*, **89**, 1890-3.

Serebriakov NB, Novik AA, Shamanskih SV, et al (1998). Diagnostic and prognostic value of interleukin-6 in malignant non-Hodgkin's lymphomas. *Vestn Ross Akad Med Nauk*, **10**, 32-6.

Seymour JF, Talpaz M, Cabanillas F, Wetzler M, Kurzrock R (1995). Serum interleukin-6 levels correlate with prognosis in diffuse large-cell lymphoma. *J Clin Oncol*, **13**, 575-82.

Seymour JF, Talpaz M, Hagemeister FB, Cabanillas F, Kurzrock R (1997). Clinical correlates of elevated serum levels of interleukin 6 in patients with untreated Hodgkin's disease. *Am J Med*, **102**, 21-8.

Seymour JF, Talpaz M, Hagemeister FB, Cabanillas F, Kurzrock R (1997). Clinical correlates of elevated serum levels of interleukin 6 in patients with untreated Hodgkin's disease.

Am J Med, **102**, 21-8.
Shipp M, Harrington D, Anderson J (1993). A predictive model for aggressive non-Hodgkin's lymphoma: the international non-Hodgkin's lymphoma prognostic factors Project. *N Engl J Med*, **329**, 987-94.
Stasi R, Zinzani L, Galieni P, et al (1994). Detection of soluble interleukin-2 receptor and interleukin-10 in the serum of patients with aggressive non-Hodgkin's lymphoma. Identification of a subset at high risk of treatment failure. *Cancer*, **74**, 1792-800.
Suda T, O'Garra A, MacNeil I, et al (1990). Identification of a novel thymocyte growth-promoting factor derived from B cell lymphomas. *Cell Immunol*, **129**, 228-40.
Suri C, McClain J, Thurston G, et al (1998). Increased vascularization in mice overexpressing angiopoietin-1. *Science*, **282**, 468-71.
Teicher BA, Holden SA, Ara G, et al (1994). Potentiation of cytotoxic cancer therapies by TNP-470 alone and with other anti-angiogenic agents. *Int J Cancer*, **57**, 920-5.
Tewari A, Buhles WC Jr, Starnes HF Jr (1990). Preliminary report: effects of interleukin-1 on platelet counts. *Lancet*, **336**, 712-14.
Urosevic M, Dummer R (2003). HLA-G and IL-10 expression in human cancer-different stories with the same message. *Semin Cancer Biol*, **13**, 337-42.
Van Snick J (1990). Interleukin-6: an overview. *Annu Rev Immunol*, **8**, 253-78.
Yee C, Biondi A, Wang XH, et al (1989). A possible autocrine role for interleukin-6 in two lymphoma cell lines. *Blood*, **74**, 798-804.
Yoshizaki K, Matsuda T, Nishimoto N, et al (1989). Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood*, **74**, 1360-7.