Concentration of interleukin-6 (Il-6), interleukin-8 (Il-8) and interleukin-10 (Il-10) in blood serum of breast cancer patients

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Abstract

Purpose: Interleukins may stimulate cancer cells growth and contribute to locoregional relapse as well as metastasis. Permanent synthesis and release of these cytokines leads to augmentation of their serum concentration that might be utilized as a marker of immunity status and immune system activation in prognosis and monitoring of the course of cancer.

Material and methods: Therefore, in the present study we assessed the concentration of IL-6, IL-8 and IL-10 in blood serum of breast cancer patients to determine whether it correlates with the disease progression.

Results: We showed statistically higher serum concentrations of IL-6, IL-8 and IL-10 in breast cancer patients in comparison with healthy women, which also correlated with clinical stage of breast cancer.

Conclusions: The present study indicates that elevated IL-6, IL-8, and IL-10 serum concentration, are strongly associated with breast cancer and correlate with clinical stage of disease. It was feasible that it can be used to diagnose women with breast cancer and to identify patients with a poor prognosis who may benefit from more aggressive management.

Key words: interleukin-6, interleukin-8, interleukin-10, breast cancer.

Introduction

Breast cancer is the most common cause of cancer-related deaths in women in industrialized nations and creates a significant public health problem. In Poland, over 11 000 new cases are diagnosed annually with 7 000 deaths attributed to this disease each year. The current trend in the incidence is expected to grow well into 21st century, despite strategies and campaigns aimed at risk factor reduction. Although significant improvements in therapy have occurred last years, most deaths from breast cancer are still caused by metastases that are resistant to conventional treatment. Therefore, novel approaches to the management of breast cancer must be developed.

The biology of breast cancer is complex, involving oncogenesis, evasion of host immune defense mechanisms, angiogenesis, invasion and metastasis. Recently, the contribution of interleukins, pleiotropic cytokines, to cancer progression has been demonstrated. IL-6, IL-8 and IL-10 exert a variety of effects on the immune system, acute-phase responses and hematopoiesis. Macrophages, monocytes and lymphocytes as well as cancer cells have been documented to produce and secrete IL-6, IL-8 and IL-10 [8,15,19]. These cytokines in an autocrine or paracrine manner induce in vitro growth of ovarian cancer, cervical cancer, prostate cancer, lung cancer, kidney cancer and melanoma cells [4,6,7,14]. Furthermore, their contributions to the tumor angiogenesis have been reported [3,9]. Moreover, it has been shown that treatment effectiveness and prognosis in course of malignancy are determined by the stage of the disease and activity of the immune system mechanisms modulated by different interleukins, e.g. IL-6, IL-8, IL-10 [10,16,20].

Therefore, in the present study we assessed the concentrations of IL-6, IL-8 and IL-10 in blood serum of breast cancer patients and healthy women and their correlation with clinical stage of breast cancer.

Material and methods

Analysis was performed in 45 breast cancer patients, diagnosed in Regional Cancer Center in Bialystok. Age of the patients ranged from 25 to 79 years. Clinical diagnosis was routinely confirmed by the histopathological examination of

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Table 1. IL-6, IL-8 and IL-10 serum concentration values in breast cancer patients and control group.

		Control group N=25	Breast cancer patients N=45
IL-6 concentration (pg/ml)	Median	3.3*	31.7*
	Range	1.56-8.6	6.25-100.0
	Percentage of elevated values	0	39 (86.7)
IL-8 concentration (pg/ml)	Median	5.2	40.1*
	Range	3.9-8.0	7.80-76.0
	Percentage of elevated values	0	36 (80.0)
IL-10 concentration (pg/ml)	Median	5.7	24.7*
	Range	3.9-8.8	5.6-37.0
	Percentage of elevated values	0	35 (77.8)

* – statistically significant differences ($p<0.05$)

Table 2. IL-6, IL-8 and IL-10 serum concentration values in breast cancer patients according to the clinical stage of the disease (TNM classification).

		Stage of the disease according to TNM classification			
		II A N=6	II B N=23	III A N=12	III B N=4
IL-6 concentration (pg/ml)	Median	18.7*	19.3*	40.9*	44.1*
	Range	6.25-30.6	7.8-36.4	7.8-96.0	8.4-100.0
	Number of patients with elevated values	5/6	20/23	11/12	3/4
IL-8 concentration (pg/ml)	Median	33.6	35.2	36.3	48.8
	Range	7.8-60.0	7.8-76.0	7.8-60.0	8.0-75.0
	Number of patients with elevated values	4/6	18/23	11/12	3/4
IL-10 concentration (pg/ml)	Median	18.9	19.6	29.9	26.0
	Range	5.6-29.0	6.4-32.0	6.2-35.0	6.9-37.0
	Number of patients with elevated values	5/6	18/23	9/12	3/4

* – statistically significant differences ($p<0.05$)

the tumor tissue samples. Of the 45 patients, 30 has suffered from ductal infiltrating carcinoma (carcinoma ductale infiltrans) and 15 from lobular infiltrating carcinoma (carcinoma lobulare infiltrans). Examined patients were in clinical stage IIA, IIB, IIIA and IIIB according to TNM classification. At the time of examination patients were not showing any signs of clinically overt active inflammatory process. Control group comprised 25 healthy women. Blood samples were collected before treatment initiation. Blood serum was stored in a freezer at -20°C.

Interleukin-6, -8 and -10 concentrations were determined in serum samples by enzyme-linked immunosorbent assays (ELISAs). ELISA reagents have been used that are commercially available in assay kits (R&D Systems). Median interleukins serum concentrations obtained from control group of healthy women were taken as reference values.

Statistical differences were analyzed by Student's t test and nonparametric Wilcoxon test. A value of $p<0.05$ was considered statistically significant.

Results

Tab. 1 presents serum concentrations of IL-6, IL-8 and IL-10 in breast cancer patients and healthy women (control group), respectively. With reference to the control group differences were considered statistically significant. Serum concentration of the IL-6 were increased in 39 (86.7%), IL-8 in 36 (80%) and IL-10 in 35 (77.8%) patients. The positive significant correlation between serum concentrations of the IL-6 and IL-8 ($p<0.05$) and negative significant correlation between serum concentrations of the IL-10 and interleukins IL-6 and IL-8 ($p<0.05$) was demonstrated. The distribution of the interleukins serum concentration according to the clinical stages of breast cancer is shown in *Tab. 2*. Higher serum concentrations of IL-6, IL-8 and IL-10 were seen in stage III of the disease compared to values obtained from stage II patients. Statistically significant differences were seen only with reference to the IL-6 serum concentration ($p<0.05$), whereas IL-8 and IL-10 serum concentrations were not significantly correlated with the stage of the disease.

Discussion

The main cause of death of breast cancer patients initially treated with radical surgery and/or radiotherapy is almost inevitable local or distant disease relapse. Recently a contribution of immune system disturbances to cancer cells growth and metastasis has been demonstrated. Presence of malignancy triggers interleukins cascade responsible for the modulation of activity of the whole immune system. IL-6, IL-8 and IL-10 profoundly affect immune response mechanisms [13,15]. These interleukins, produced by immunocompetent cells as well as cancer cells, exert their effects on various host cell types resulting in a variety of biologic responses, such as induction of proliferation and differentiation of immunocompetent cells or induction of acute-phase proteins [13]. Interleukins may also stimulate cancer cells growth and contribute to locoregional relapse as well as metastasis [4,5,7]. Permanent synthesis and release of these cytokines lead to augmentation of their serum level that might be utilized as a marker of immunity status and immune system activation in prognosis and monitoring of the course of cancer. Recently, a various aspects of clinical utilization of interleukins serum levels in ovarian cancer, cervical cancer, prostate cancer, kidney cancer and lung cancer have been evaluated [3,7,20]. It has been showed that breast cancer cells lines are able to produce and secrete IL-6, IL-8 and IL-10 [11]. However, results obtained by different authors clinically are somewhat inconsistent. Some authors [17,18,21] reported elevated IL-6 and IL-8 serum concentration before treatment initiation as indicators of poor prognosis in breast cancer patients. Others [10,16] did not reveal such dependence. Thus, clinical value of these interleukins serum concentration monitoring in breast cancer patients remains to be fully elucidated.

In the present study it has been demonstrated that breast cancer is associated with elevated serum concentrations of IL-6 and IL-8 that are known stimulators of angiogenesis as well as cancer cells proliferation and growth [1,9]. Moreover, significantly higher serum concentrations of IL-10 in breast cancer patients compared to control group subjects have been documented. In addition, high values of IL-10 serum concentration were associated with low serum concentrations of IL-6 and IL-8, whereas elevated values of IL-6 and IL-8 serum concentration were detected in breast cancer patients with confirmed low serum concentration of IL-10. Interleukin-10 is a multifunctional cytokine that may inhibit both immune cellular-type response and Th-1 (CD4 +) – mediated functions of immunocompetent cells that are able to produce IL-6 and IL-8 leading to the progression of malignancy [2,12,15]. Convincingly, host immune response as well as interleukins production by cancer cells resulting in increased values of IL-6, IL-8 and IL-10 serum concentration in advanced breast cancer patients.

In summary, the present study indicates that elevated IL-6, IL-8 and IL-10 serum concentration are strongly associated with breast cancer and it also correlate with clinical stage of disease. This can be possibly used to diagnose women with breast cancer and to identify patients with a poor prognosis who may benefit from more aggressive management.

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