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HIGH LEVELS OF PROINFLAMMATORY CYTOKINES TUMOR NECROSIS FACTOR ALPHA, INTERLEUKIN 1β AND INTERLEUKIN 6 IN BONE MARROW AND PERIPHERAL BLOOD OF BREAST CANCER PATIENTS AS PREDICTORS OF RELAPSE

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Breast cancer provides a typical example of an inflammation-linked malignant disease. The inflammatory components present in the tumor microenvironment contribute to the further progression of the disease. The present study was conducted to evaluate the correlation between levels of proinflammation cytokines tumor necrosis factor α, interleukin 1β, interleukin 6, C-reactive protein and tumor recurrence in breast cancer patients. Seventy two breast cancer patients with histologically proven diagnosis and 15 healthy donors were enrolled into study. Thirty one patients with progression of the disease and 41 patients with clinical stabilization (conditional remission) were included to “progression” and “remission” groups respectively. This division of breast cancer patients was made during the 3 years study. The levels of proinflammation cytokines – tumor necrosis factor α, interleukin 1β, interleukin 6 and C-reactive protein were revealed. This cytokines in bone marrow and peripheral blood act as a specific microenvironment and was found that the elevated levels of this cytokines were strongly associated with progression of breast cancer. The data showed that most prominent predictive markers of tumor recurrence are high levels of indicated cytokines in combination with other markers (C-reactive protein; disseminated tumor cells in bone marrow). Determination of the high levels of tumor necrosis factor, interleukin 1β, interleukin 6 in bone marrow and peripheral blood of breast cancer patients are important to establish the features of bone marrow microenvironment for prediction of metastasis and correction antitumor therapy.

Keywords: breast cancer, proinflammatory cytokines, bone marrow, peripheral blood, disseminated tumor cells.

INTRODUCTION

Inflammatory pathways have garnered considerable interest as an important mediator of the molecular mechanisms leading to carcinogenesis. The link between inflammation and cancers was noticed near 150 years ago by Virchow [1]. Breast cancer provides a typical example of an inflammation-linked malignant disease. It is known that the development of cancers from inflammation might be a process driven by inflammatory cells and variety of mediators such as cytokines and chemokines which altogether form the part of tumor microenvironment [15]. Breast tumors are enriched with inflammatory constituents, including cells that are polarized to the tumor-promoting phenotype, and soluble factors. The results of many studies indicate that many of the inflammatory components present in the tumor microenvironment actively support breast cancer development and progression [19]. The 'inflammation–cancer' connection is not restricted to increased risk for a subset of tumors. An inflammatory component is present in the microenvironment of most neoplastic tissues, including those not causally related to an obvious inflammatory process. Key features of cancer-related inflammation include the infiltration of leukocytes, prominently tumor-associated macrophages; the presence mediators of inflammation: cytokines (tumor necrosis factor, interleukin 1 and interleukin 6), and chemokines (CCL2 and CXCL8) and the occurrence of tissue remodeling and angiogenesis [3]. A large body of evidence suggests that high levels of tumor-associated macrophages are correlated with poor prognosis in breast carcinoma. Many studies have shown a positive relationship between high levels of tumor-associated macrophages and lymph node metastases in breast carcinoma, and suggested that the density of tumor-associated macrophages is associated with clinical aggressiveness [4, 12]. The tumor-promoting activities of tumor-associated macrophages may be the result of their ability to express numerous tumor-promoting characteristics, such as growth factors for breast tumor cells, angiogenic mediators, extracellular matrix degrading enzymes and inflammatory cytokines [2]. Cytokines, including interleukins, tumor necrosis factor, different growth factors, and differentiation factors (colony-stimulating factors), are secreted or membrane-bound molecules that play a regulatory role in growth, differentiation, and activation of immune cells. Cytokine signaling could contribute to the progression of tumors in two aspects: the stimulation of cell growth and differentiation and the inhibition of apoptosis of altered cells at the inflammatory site [5, 14].

Tumor necrosis factor, interleukin 1β and interleukin 6 are cytokines of systemic action which has been shown to be associated with tumor progression and metastasis. This suggests that investigation of the levels of tumor necrosis factor, interleukin 1β and interleukin 6 in bone marrow and peripheral blood of breast cancer patients might be additional predictive factors of tumor recurrence and further correction antitumor therapy with the inclusion of anti-inflammatory drugs.

MATERIALS AND METHODS

Patients. The population under study comprised of 72 breast cancer patients Rivne Region Oncology Hospital (Rivne, Ukraine) and 15 healthy donors. Majority of the patients was in the age group of 40–59 years; healthy donors – 33–62 years. Breast cancer patients were divided in two groups: 1) with progression of disease (31 patients), and 2) with clinical stabilization (conditional remission) (41 patients) according to the definition of the WHO Expert Committee of the terms "progression" of cancer and "remission". This

division of breast cancer patients was made during 3 years study. 29 breast cancer patients with metastatic bone lesions constituted a risk group were received two variant of treatment: variant A (radiotherapy, bisphosphonates, non-steroidal anti-inflammatory drugs and antibiotics) – 15 patients and variant B (radiotherapy and bisphosphonates) – 14 patients. All breast cancer patients before treatment were randomized by the TNM classification, age, histological structure of the tumor, steroid hormone receptor status, and level of HER-2/neu expression in tumor cells. In this study, BC patients consisted of only II (45 patients) and III (27 patients) stages. They were informed about the survey and provided consent to the use of the material for research purposes. The study was carried out with approval of the Ethics Committee of the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, NAS of Ukraine.

Various parameters that were evaluated include detailed clinico-pathological profile, proinflammation cytokines levels (tumor necrosis factor, interleukin 1β and interleukin 6). The level of C-reactive protein and erythrocyte sedimentation rate in peripheral blood of these breast cancer patients was investigated before and after therapy.

Blood and bone marrow samples. The bone marrow aspirates (3–4 ml) was carried out from sternum with an incision in the skin in the sampling area to avoid contamination by the epithelial cells. Blood samples (5–9 ml) were obtained by venipuncture. Samples of bone marrow and peripheral blood from breast cancer patients were obtained before treatment.

Venous blood and aspirates of bone marrow were collected for plasma preparation into test tubes with EDTA (Sente-Lab, Ukraine). The plasma samples were centrifuged (10 min, 8000 rpm, +4 °C) (Microspin, Eppendorf, USA) to quantitatively remove residual platelets as possible source of different cytokines and stored frozen at -20 °C.

Erythrocyte sedimentation rate evaluation. Erythrocyte sedimentation rate was evaluated by using standard method. The pipettes with blood to stand in vertical position and precisely after 1 hour and 2 hours should read the lower value of the plasma column was registered. The result should be written in the form: Erythrocyte sedimentation rate = mm of plasma column after 1 hour/mm of plasma column after 2 hours of investigation.

Bioassay tests. Detection levels of tumor necrosis factor and it's biological activity in experimental samples (plasma of bone marrow and of peripheral blood) of breast cancer patients were determined by means of sensitive bioassay tests using of L929a cell line [11]. The results of experiments were obtained by the crystal violet assay and recorded by using microplate reader (Labsystems Multiskan PLUS, Finland) at a wavelength of 540 nm.

L929a cells were cultured in the RPMI-1640 medium (PAA, Austria) with 10 % newborn calf serum (Sigma, USA) at 37 °C and 5 % of CO_2. The cells were seeded in 96-well plate in concentration $1{,}5\times10^4$ per well and cultivated for 24 hours at 37 °C and 5 % of CO_2. After that, experimental samples and standard of tumor necrosis factor (Recombinant Human tumor necrosis factor-alpha (Chemicon International, USA)) were added. After incubation for 24 hours at 37 °C in 5 % CO_2, the viable cells were quantified by the crystal violet assay.

Crystal violet test. Assessment of the proliferative activity of the cells after 48 hours incubation with test samples was performed using colorimetric crystal violet test (Sigma, USA) [25].

ELISA assay. The levels of interleukin 1β and interleukin 6 were determined by the receptor-based Quantikine ELISA Kit (Demeditec, Germany and eBioscience, Austria, respectively), according to the manufacturers instruction. The absorbance at 450 nm was detected by the microplate reader (Labsystems Multiskan Plus, Finland). Concentrations were calculated from the constructed of standard curve. The level of C-reactive protein was evaluated by using hsC-reactive protein ELISA (Biomerica, USA).

Statistics. The regression analysis was used to study possible correlation among different parameters (Statistica 7.0).

RESULTS AND DISCUSSION

Nowadays, the data about tumor markers that reliably predict prognosis independently or together with another marker (presence of disseminated tumor cells in bone marrow) are not sufficient. In this respect, most promising is to determine the levels of certain cytokines associated with tumor progression that may serve as factors of disease recurrence. The levels of proinflammatory cytokines in bone marrow and peripheral blood of breast cancer patients might be more prominent markers which play key roles in different stages of tumor growth and are associated with progression of disease.

Tumor necrosis factor is a bidirectional cytokine which has been found to have procancerous and antitumor effects [26, 24]. In our study it was established that tumor necrosis factor is an active modulator of metastatic potential tumor cells: the action of tumor necrosis factor toward tumor cell was accompanied by a possibility of metastasis depending on cellular type, concentration of that cytokine and duration of tumor necrosis factor action. Additionally, *in vivo* entering of tumor necrosis factor created conditions to stimulation of metastasis process in early stages: it increases adhesive properties of endothelial cells and impairs the endothelial layer of blood capillaries [8, 9]. An expression of tumor necrosis factor is minimal in normal mammary epithelial cells and is simultaneously acquired by the cells during malignant transformation. Besides, tumor necrosis factor induces epithelial-mesenchymal transition in the tumor cells which facilitating metastasis process via a loss of epithelial cells their cell polarity and cell-cell adhesion, and gaining migratory and invasive properties. Activation of these features forms a highly metastatic phenotype and makes it at the most closer to stem cells with high level of drug resistance.

It is well known that in normal blood of healthy donors tumor necrosis factor is missing or does not exceed the level of 10–12 pg/ml. Bioactive tumor necrosis factor in samples of bone marrow and peripheral blood from healthy donors is not detected. Our study has shown that the level of tumor necrosis factor in bone marrow and peripheral blood was increased in all breast cancer patients regardless of clinical status and was higher than 50 pg/ml (Tabl.1). The tumor necrosis factor level in bone marrow is higher than 100 pg/ml or 150 pg/ml in patients of progression group was revealed in 66.7 and 45.8 % cases, respectively, and only in 36.6 and 22.9 % patients of the remission group. Similarly, the same ratio was found during the analysis of tumor necrosis factor levels in peripheral blood of these breast cancer patients (Table 1). These data indicate the strong correlation between increased levels of tumor necrosis factor in bone marrow and peripheral blood of breast cancer patients and tumor progression. It should be noted that the average level of this cytokine in bone marrow and peripheral blood of breast cancer patients of remission group, usually did not exceed 100 pg/ml.

Table 1. **The level of tumor necrosis factor in bone marrow and peripheral blood of breast cancer patients**

Таблиця 1. **Рівень фактора некрозу пухлин у кістковому мозку та периферичній крові хворих на рак молочної залози**

Groups		Tumor necrosis factor		
		average level (pg/ml)*	% cases (>100 pg/ml)	% cases (>150 pg/ml)*
Progression (n=31)	*bone marrow*	198.7±25.3**	66.7	45.8
	peripheral blood	138.6±19.7**	42.1	36.8
Remission (n=41)	*bone marrow*	97.7±8.8**	36.6	22.9
	peripheral blood	81.9±4.9**	8.7	8.7
Healthy donors (n=15)	*bone marrow*	0	0	0
	peripheral blood	0	0	0

Comments: * – data published in [16]; **– p < 0.01 Cox regression analysis.

Примітки: *– дані опубліковані [16]; ** – p < 0,01 регресійний аналіз за Коксом.

The levels of tumor necrosis factor were different in breast cancer patients with and without presence of disseminated tumor cells in bone marrow (with distant metastasis). Thus, the level of tumor necrosis factor in bone marrow of breast cancer patients with disseminated tumor cells in bone marrow (progression group) was 360.0±34.2 pg/ml and without disseminated tumor cells in bone marrow it was 225.0±23.7 pg/ml [17]. The level of tumor necrosis factor in bone marrow and peripheral blood from II to III stages of the disease in patients of progression group increased (p < 0.01) [16].

Interestingly, the proinflammatory cytokines play an important role in potentiating the inflammatory cascade, and they are significantly elevated in metastatic breast cancer patients. Blood plasma triggers an adhesive phenotypic switch of breast cancer cells and interleukin 6 and tumor necrosis factor induce the adhesive recruitment of the breast cancer cells [6].

This demonstrates an importance of determining the level of this cytokine in the peripheral blood and bone marrow breast cancer patients as an additional prognostic marker of the breast cancer recurrence in a combination with the detection disseminated tumor cells in bone marrow.

The role of two other inflammatory cytokines, interleukin 6 and interleukin 1β, was also studied in breast carcinoma. Initial analysis regarding interleukin 1β indicated that its level was significantly higher in an invasive carcinoma than in ductal carcinoma *in situ* or the benign lesions, implying that elevated levels of interleukin 1β directly correlated with more advanced disease [2]. The recent studies [22] suggest that elevated levels of interleukin 6 may contribute to disease progression.

Interleukin 1β is a pleiotropic cytokine with a wide range of functions that include induction of other growth factors and the regulation of receptor expression. Interleukin 1 includes two different proteins – interleukin 1α and interleukin 1β, which play a major role in acute and chronic inflammation, both at local and systemic level. Interleukin 1 is produced by monocytes and macrophages, endothelial and T cells, as well as fibroblasts [18].

In our study, the analysis of interleukin 1β in the bone marrow and peripheral blood of breast cancer patients has shown that this factor was not detected in peripheral blood of healthy donors. The level of this factor in bone marrow of patients of the progression

group was almost 2.5 times higher compared with that in the patients of the remission group (Table 2). However, a significant difference between the levels of this factor in peripheral blood of breast cancer patients of progression group and of remission group was not found. Interestingly, this cytokine was not detected in bone marrow and peripheral blood of some breast cancer patients regardless of the clinical status of the disease. However, number of these breast cancer patients with stabilization of tumor process was higher (Table 2). Thus, the number of breast cancer patients with absent interleukin 1β in bone marrow was 18 % (progression group) and 31 % (remission group). Similar situation was observed at determination of cytokine in peripheral blood. This may indicate the importance of measuring individual level of interleukin 1β in each case, and always in combination with other humoral factors (tumor necrosis factor, interleukin 6) which are linked to the performance of certain biological functions and thus, determine specific microenvironment for tumor cells. Moreover, interleukin 1β together with tumor necrosis factor has certain characteristics: promote interaction between leukocytes and the endothelium of blood vessels inducing cytokine production. Elevated content of interleukin 1β correlated with relapse in breast cancer patients and is associated with tumor invasiveness and more aggressive phenotype of tumor cells [13].

Table 2. **The level of interleukin 1β in bone marrow and peripheral blood of breast cancer patients**

Таблиця 2 . **Рівень інтерлейкіну 1β у кістковому мозку та периферичній крові хворих на рак молочної залози**

Groups		Interleukin 1β average level, pg/ml	% patients without interleukin 1β
Progression (n=31)	*bone marrow*	3.27±0.85*	18
	peripheral blood	0.66±0.11	57.1
Remission (n=41)	*bone marrow*	1.34±0.31*	31
	peripheral blood	1.1±0.21	75
Healthy donors (n=15)	*peripheral blood*	0	–

Comment: *– $p < 0.05$.

Примітка: * – $p < 0,05$.

Interleukin 6 is a proinflammatory cytokine with a wide range of functions including the regulation of immune responses, inflammation, and hematopoiesis. It has been shown that interleukin 6 is associated with tumor progression and metastasis, including inhibition of apoptosis of tumor cells and stimulation of angiogenesis, as well as an adhesion of the disseminated tumor cells. This cytokine is considered as a potential prognostic factor in cancer [22].

We have found that level of interleukin 6 in peripheral blood of healthy donors was 1.02±0.26 pg/ml. This value correlates well with data presented in other publications – 2.03 pg/ml [10] and 3.3 pg/ml [7]. Besides, our investigation has shown that mean level of interleukin 6 in peripheral blood of breast cancer patients in the progression group was 1.2 times higher compared with that in patients of the remission group (Table 3). The level of this cytokine was significantly increased in peripheral blood of all breast cancer patients (7.11 times in patients with a progression of the disease and 5,85 times in patients with the stabilization of process) compared to that in healthy donors. In bone

marrow of these patients, regardless of the clinical course of the disease, an increasing level of interleukin 6 was observed compared with the control one. However, significant differences between the levels of interleukin 6 in bone marrow of breast cancer patients of different groups have not been identified. An increased serum level of interleukin 6 has been demonstrated in breast cancer patients compared to healthy donors which correlates with advanced breast tumor grade and increased number of metastatic sites [20]. Recent studies have shown that interleukin 6 is a factor of regulation and modulation of tumor-mediated bone destruction. It is known that metastasis to the bone occurs in various types of cancer including breast cancer, prostate, lung or kidney cancer, melanoma or neuroblastoma. Thus, the development of metastases in bone of breast cancer patients occurs in 60–75 % of patients with the metastatic cancer. The integrity of the bone is broken when tumor cells metastasis which leading to the creation of pathological conditions. The one of important features of this process is to enhance interleukin 6 expression by tumor cells, activation of bone stromal cells and infiltration by monocytes and macrophages. All these events lead to an increased activity of osteoclasts that facilitates tumor cell invasion and metastasis development [23]. Recently, interleukin 6 has been observed as a prognostic factor for prostate cancer and breast cancer. The level of interleukin 6 in blood serum is significantly increased in many patients with prostate cancer compared with that in patients with benign disease. Similarly increased level was observed in the case of distant metastases in breast cancer patient and prostate cancer compared with that in patients without metastases. Elevated levels of interleukin 6 were associated with a decrease in survival of patients with metastatic prostate and breast cancer. Moreover, interleukin 6 promotes breast cancer cell growth and epithelial-mesenchymal transition in breast cancer cells [21].

Table 3. **The level of interleukin 6 in bone marrow and peripheral blood of breast cancer patients**

Таблиця 3. **Рівень інтерлейкіну 6 у кістковому мозку та периферичній крові хворих на рак молочної залози**

Groups		Interleukin 6
		average level, pg/ml
Progression (n=31)	bone marrow	3.91±1.11
	peripheral blood	7.26±0.74
Remission (n=41)	bone marrow	3.61±1.03
	peripheral blood	5.97±0.51
Healthy donors (n=15)	peripheral blood	1.02±0.26

Of great interest is the fact that two cytokines (interleukin 6 and interleukin 1) and tumor necrosis factor are interrelated and may form a network of factors that may affect tumor cell progression in a cooperative manner.

Other factors such as C-reactive protein levels and erythrocyte sedimentation rate in peripheral blood of breast cancer patients in effectiveness of therapy have been established. High levels of circulating C-reactive protein has been recently linked to poor clinical outcome in various malignancies. An increased erythrocyte sedimentation rate was found in pathological conditions, including neoplastic processes. Based on these facts, erythrocyte sedimentation rate and C-reactive protein levels in peripheral blood of breast cancer patients were estimated before and after treatment with two courses of therapy (variant A and variant B) (Fig. 1). C-reactive protein level was found to be more prominent risk factor

associated with bone metastasis in breast cancer patients (Fig. 1, *B*). Its level was decreased after variant A of treatment with non-steroidal anti-inflammatory drugs. The same decrease of erythrocyte sedimentation rate was observed in variant A of therapy compared with variant B (Fig.1, *A*). These data indicate an importance of correction antitumor therapy according to measured C-reactive protein levels and enhanced levels of certain cytokines (tumor necrosis factor) in a combination with detection disseminated tumor cells in bone marrow. A complex of these factors might be useful to form groups of breast cancer patients with an increased risk of relapse.

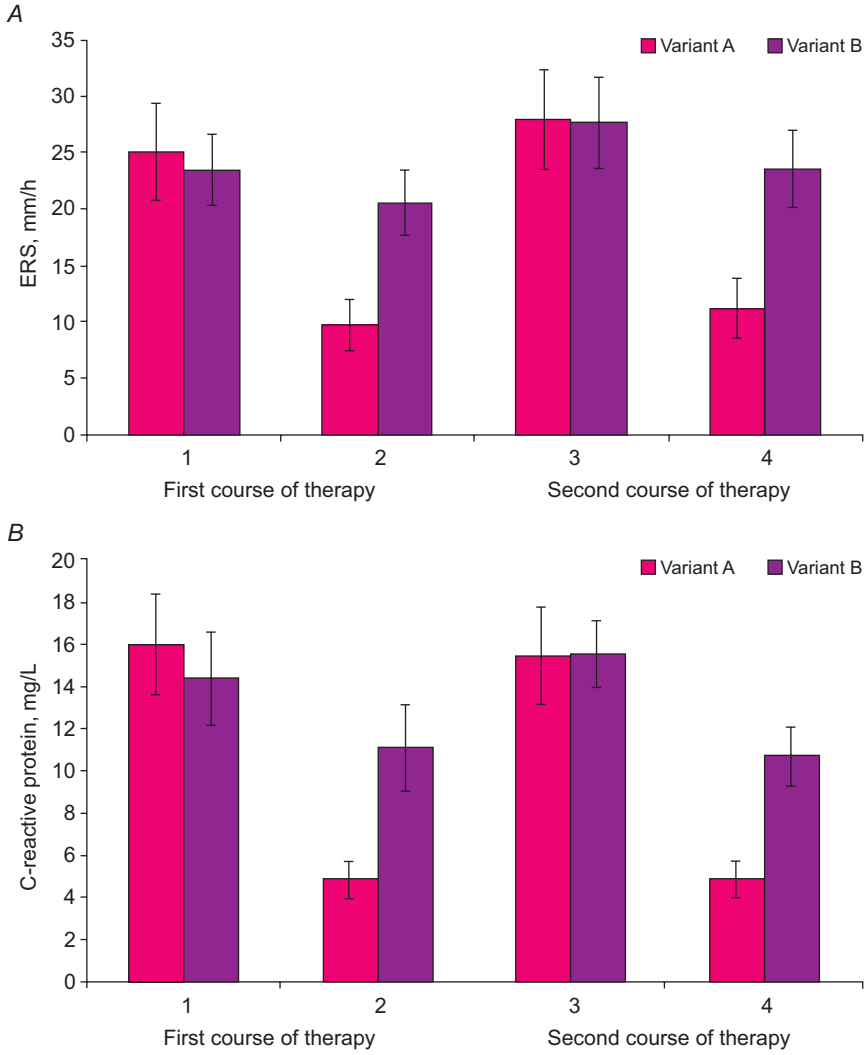

Fig. 1. Erythrocyte sedimentation rate (*A*) and C-reactive protein level (*B*) in peripheral blood of breast cancer patients before (1 and 3) and after (2 and 4) treatment at two course of therapy (variant *A* and variant *B*)

Рис. 1. Швидкість осідання еритроцитів (*A*) і рівень С-реактивного білка (*B*) в периферичній крові хворих на рак молочної залози до (1 і 3) і після (2 і 4) лікування протягом двох курсів терапії (варіант *A* і варіант *B*)

CONCLUSION

The identification of cytokine status peripheral blood and bone marrow of breast cancer patients, especially of the levels of proinflammatory cytokines such as, tumor necrosis factor, interleukin 1β and interleukin 6, may be considered as a complex of prognostic markers of tumor recurrence (distant metastases) that will be base for the subsequent correction of treatment regimen in individual patient.

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. We also certify that this study involving human subjects was performed in accordance with the Helsinky Declaration of 1975, revised in 2000, and it has been approved by the relevant institutional Ethical Committee.

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ВИСОКИЙ РІВЕНЬ ПРОЗАПАЛЬНИХ ЦИТОКІНІВ ФАКТОРА НЕКРОЗУ ПУХЛИН АЛЬФА, ІНТЕРЛЕЙКІНУ 1β ТА ІНТЕРЛЕЙКІНУ 6 У КІСТКОВОМУ МОЗКУ ТА ПЕРИФЕРИЧНІЙ КРОВІ ХВОРИХ НА РАК МОЛОЧНОЇ ЗАЛОЗИ ЯК ПРОГНОСТИЧНИЙ ФАКТОР РЕЦИДИВУ ЗАХВОРЮВАННЯ

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Рак молочної залози є типовим прикладом злоякісного захворювання, пов'язаного із запаленням, компоненти якого в пухлинному мікрооточенні сприяють не лише виживаності та проліферації пухлинних клітин, але й прогресуванню захворювання. Метою цього дослідження було оцінити кореляцію між рівнями прозапальних цитокінів (фактор некрозу пухлин альфа, інтерлейкін 1β та інтерлейкін 6) у кістковому мозку і периферичній крові, рівнем С-реактивного білка (у периферичній крові) та виникненням рецидиву захворювання у хворих на рак молочної залози. У дослідження були включені 15 здорових донорів і 72 хворі на

рак молочної залози, які були поділені на 2 групи (група прогресії – 41 пацієнтка, група ремісії – 31 пацієнтка). Такий поділ був зроблений за результатами 3-річних досліджень. Встановлено, що підвищений рівень прозапальних цитокінів у кістковому мозку та периферичній крові хворих на рак молочної залози тісно пов'язаний із прогресуванням процесу. З'ясовано, що найбільш перспективними прогностичними маркерами виникнення рецидиву є високі рівні даних цитокінів у комплексі з іншим фактором прогнозу (дисеміновані пухлинні клітини в кістковому мозку). Визначення рівня фактора некрозу пухлин альфа, інтерлейкіну 1β та інтерлейкіну 6 у кістковому мозку і периферичній крові хворих на рак молочної залози є важливим показником прогнозу виникнення метастазів та корекції протипухлинної терапії.

Ключові слова: рак молочної залози, прозапальні цитокіни, кістковий мозок, периферична кров, дисеміновані пухлинні клітини.

ВЫСОКИЙ УРОВЕНЬ ПРОВОСПАЛИТЕЛЬНЫХ ЦИТОКИНОВ ФАКТОРА НЕКРОЗА ОПУХОЛИ АЛЬФА, ИНТЕРЛЕЙКИНА 1β И ИНТЕРЛЕЙКИНА 6 В КОСТНОМ МОЗГЕ И ПЕРИФЕРИЧЕСКОЙ КРОВИ БОЛЬНЫХ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ КАК ПРОГНОСТИЧЕСКИЕ ФАКТОРЫ РЕЦИДИВА ЗАБОЛЕВАНИЯ

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Рак молочной железы является типичным примером злокачественного новообразования, связанного с воспалением, компоненты которого способствуют не только выживаемости и пролиферации опухолевых клеток в их микроокружении, но и дальнейшему прогрессированию заболевания. Целью данного исследования было оценить корреляцию между уровнями провоспалительных цитокинов (фактор некроза опухоли альфа, интерлейкин 1β и интерлейкин 6), С-реактивного белка и возникновением рецидива заболевания у больных раком молочной железы. В исследование были включены 15 здоровых доноров и 72 больных раком молочной железы, которые были разделены на 2 группы (группа прогрессии – 41 пациентка, группа ремиссии – 31 пациентка). Такое разделение было сделано на основании результатов 3-летних исследований. Установлено, что повышенный уровень провоспалительных цитокинов в костном мозге и периферической крови больных раком молочной железы тесно связан с прогрессированием процесса. Показано, что наиболее перспективным прогностическим маркером рецидива является высокий уровень данных цитокинов в комплексе с другим фактором негативного прогноза (диссеминированные

опухолевые клетки в костном мозге). Определение цитокинового профиля, в частности уровня фактора некроза опухолей альфа, интерлейкина 1β и интерлейкина 6 в костном мозге и периферической крови больных раком молочной железы является важным этапом в установлении особенностей микроокружения в костном мозге для прогнозирования возникновения метастазов и внесения на основании этого корректив в тактику противоопухолевой терапии.

Ключевые слова: рак молочной железы, провоспалительные цитокины, костный мозг, периферическая кровь, диссеминированные опухолевые клетки.

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