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ORIGINAL ARTICLE

BLOOD LEVELS OF GROWTH AND PROGRESSION FACTORS IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER DURING NEOADJUVANT CHEMOTHERAPY

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ABSTRACT

Purpose of the study. An analysis of blood levels of TGF-β, TGFR2, TNF-α, TNF-αR1, TNF-αR2, CD44 and MMP9 in patients with various biological subtypes of breast cancer receiving neoadjuvant chemotherapy.
Materials and methods. This article presents an analysis of levels of growth and progression factors (TGF-β, TGFR2, TNF-α, TNF-αR1, TNF-αR2, CD44 and MMP9) in the blood of 162 patients with various biological subtypes of locally advanced breast cancer receiving 8 cycles of neoadjuvant chemotherapy.
Results. Levels of TGF-β, TGFR2, TNF, TNF-α, TNFR1, TNFR2, CD44, MMP9 in patients with all BC subtypes were high before the treatment. After chemotherapy cycles, the values decreased statistically significantly in all BC subtypes: CD44 decreased by 25.2 %, 30 % and 54.7 % in luminal A, luminal B and TNBC, respectively; TNFα– by 26.2 %, 48.3 % and 50.8 %, respectively; TNFα-R1 – by 52.1 %, 39.2 % and 50.3 % respectively; TNFα-R2 – by 31.7 %, 32.8 % and 41.9 % respectively; MMP9 – 35.3 %, 32.6 % and 43.3 % respectively.
Conclusions. We identified a combination of growth and progression factors which determines the chemotherapy sensitivity and resistance in all subtypes of breast cancer; so, a decline in the levels of TGF-β, TNFα, MMP9 and CD44 after neoadjuvant chemotherapy predicts further remission for at least 3 years. On the contrary, stabilization or an increase of these indicators leads to the early tumor progression.

Keywords:
breast cancer, biological subtypes, neoadjuvant polychemotherapy, growth and progression factors, IHC, remission, progression, chemotherapy resistance.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

СОДЕРЖАНИЕ ФАКТОРОВ РОСТА И ПРОГРЕССИРОВАНИЯ В КРОВИ БОЛЬНЫХ МЕСТНОРАСПРОСТРАНЕННЫМ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ В ПРОЦЕССЕ НЕОАДЪЮВАНТНОЙ ХИМИОТЕРАПИИ

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РЕЗЮМЕ

Цель исследования. Изучение уровня TGF-β, TGFR2, TNF-α, TNF-αR1, TNF-αR2, CD44 и MMP9 в крови больных раком молочной железы различных биологических подтипов, получивших неоадъювантную химиотерапию.
Материалы и методы. В работе представлены результаты исследования изучения содержания факторов роста и прогрессирования (TGF-β, TGFR2, TNF-α, TNF-αR1, TNF-αR2, CD44 и MMP9) в крови у 162 больных местнораспространенным раком молочной железы различных биологических подтипов, которым было проведено 8 курсов неоадъювантной химиотерапии.
Результаты. Уровни TGF-β, TGFR2, TNF, TNF-α, TNFR1, TNFR2, CD44, MMP9 у пациентов со всеми подтипами РМЖ были высокими до лечения. После циклов химиотерапии значения статистически значимо снизились во всех подтипах РМЖ: CD44 уменьшился на 25,2 %, 30 % и 54,7 % в люминальном А, В и TNBC соответственно; TNFα – на 26,2 %, 48,3 % и 50,8 % соответственно; TNF-αR1 – на 52,1 %, 39,2 % и 50,3 % соответственно; TNF-αR2 – на 31,7 %, 32,8 % и 41,9 % соответственно; MMP9 – 35.3 %, 32,6 % и 43,3 % соответственно.
Заключение. Выявлен комплекс факторов роста и прогрессии, определяющий чувствительность и резистентность к химиотерапии при всех подтипах РМЖ, а именно снижение уровня TGF-β, TNF-α, MMP9 и CD44 после неоадъювантной химиотерапии определяет в дальнейшем ремиссию в течение минимум 3 лет. Напротив, стабилизация или увеличение этих показателей приводит в дальнейшем к раннему прогрессированию злокачественного процесса.

Ключевые слова:
рак молочной железы, биологические подтипы, неоадъювантная полихимиотерапия, факторы роста и прогрессирования, ИГХ, ремиссия, прогрессирование, резистентность к химиотерапии.

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Despite the improvement in the 10-year overall survival rate of breast cancer patients, this disease remains the leading cause of cancer death in women worldwide. One of the main reasons is the occurrence of tumor recurrence and resistance to therapy [1]. There is increasing evidence that the aggressive nature of TNBC tumors may be due to the presence of a higher frequency of cancer stem cells (CD44 high CD24 low/-) compared to other subtypes of breast cancer [2, 3]. These observations suggest that the subgroup of cancer stem cells in tumors is heterogeneous in nature with respect to the phenotype and may function among different subtypes of breast cancer. Single-cell transcriptomic analysis of primary and metastatic tumors of various subtypes of breast cancer can certainly provide very interesting information about the heterogeneity of cancer stem cells. Such information could then provide the basis for a hypothesis about how heterogeneity in the cancer stem cell compartment in different subtypes of breast cancer can be a predictor of response to therapy and resistance to therapy.

Currently, the clinical problem in the treatment of breast cancer is the development of resistance to therapy, the progression of the disease due to the occurrence of relapses and distant metastasis. The regulation of cancer stem cell function and the induction of chemoresistance under the influence of external factors, such as cytokines, chemokines and hypoxia, become obvious as potential strategies. They can be aimed at the interaction of cancer stem cells with cellular and non-cellular components of the extracellular matrix as more effective therapeutic approaches.

The role of transforming growth factor β (TGF-β) in the regulation of tumor cell proliferation, metastasis and remodeling of the extracellular matrix is also well documented [4]. According to the literature, prolonged exposure to TGF-β on human breast epithelial cells enhances the phenotype of the epithelial-mesenchymal transition (EMT) and increases the number of CD44 cells – a known marker of stem cancer cells [5, 6]. In response to the effect of TGF-β, epithelial and carcinoma cells undergo a partial or complete epithelial-mesenchymal transition, which contributes to the progression of cancer. This process is considered reversible, because the cells return to the epithelial phenotype after removal of TGF-β. However, the authors found that long-term exposure to TGF-β contributes to stable EMT in breast epithelial cells and carcinoma, in contrast to reversible EMT caused by shorter exposure. The stabilized EMF was accompanied by a steadily increased production of stem cells and resistance to antitumor drugs.

Other cytokines, such as tumor necrosis factor alpha (TNF-α) and endothelial growth factor (EGF), regulate the activity of cancer stem cells. When tumor cells from the luminal A subtype of breast cancer were exposed to TNF-α, the population of breast cancer cells became enriched for the CD44+ CD29+ CSC phenotype with increased metastatic properties [7]. Further studies should be conducted to assess the content of TNF-α and their receptors in the serum of various subtypes of breast cancer before and after standard treatment [8].

Cancer biomarker research can play an important role in areas such as cancer diagnosis and prediction, monitoring of disease progression, predicting disease recurrence, monitoring and predicting treatment effectiveness, and cancer screening. According to some studies, the level of expression of p53 protein receptors in luminal subtypes is different. In hormone-positive tumors, a high level of p53 expression is associated with overexpression or mutation of Her2neu [9]. It was found that MMR9 is a potential biomarker for several types of cancer [10, 11]. It can be used as a marker in areas such as diagnosis, monitoring the effectiveness of treatment and monitoring the progression of the disease. Some biomarkers may not have sufficient specificity for clinical applicability when they are used as a single marker. The use of a combination of biomarkers is one of the strategies for increasing their specificity. To achieve this goal, MMR9 can also be used in combination with other cancer biomarkers [9].

The purpose of the study: the study of the level of TGF-β, TGFR2, TNF-α, TNF-αR1, TNF-αR2, CD44 and MMR9 in the blood of breast cancer patients of various biological subtypes who received neoadjuvant chemotherapy.

MATERIALS AND METHODS

The study included data on 162 patients with locally advanced primary inoperable Her2 negative stage III breast cancer aged 30 to 65 years, having a somatic status on the ECOG-WHO scale from 0 to 1 points (on the Karnovsky scale from 100 % to 80 %). After the diagnosis and comprehensive treatment, the patients were monitored, according to the results of which they were divided into 2 groups. The first group consisted of data on 58 patients who had previously experienced disease progression (local relapse or distant metastasis) in the period from 6 to 12 months. The second group included 104 patients who had remission after treatment for at least 3 years (36 months).

According to the biological subtype, the patients were distributed as follows: in group 1 there were 58.62 % (34) patients who were diagnosed with a thrice-negative variant of the tumor, in 41.38 % (24) patients-a luminal negative subtype in Her2. Luminal A subtype was not observed in any patients in group 1; hormone-dependent subtypes of the tumor were most common in group 2 (82 patients – 78.85 %). Luminal B, Her2 negative subtype was diagnosed in 40 patients (38.46 %), luminal A subtype – in 42 patients (40.39 % of cases). Also, 21.15 % (22 patients) were diagnosed with a triple-negative variant of the tumor.

The following levels were determined in the blood serum of patients using standard ELISA test systems: TGF-β1, TNF-α, CD44, MMR9 (BenderMedSystem, Austria); TGF-βRII (RayBiotech, USA); TNF-αRI and TNF-αRI (R&D systems, USA&Canada).

Statistical data processing was performed using the STATISTICA 10 statistical package (StatSoft Inc., USA). Descriptive statistics of quantitative features are presented in the form of the arithmetic mean and the standard error of the arithmetic mean (M±s). The reliability of the differences between the samples was evaluated using the nonparametric Mann-Whitney test (the differences were considered reliable at $p<0.05$).

RESEARCH RESULTS AND DISCUSSION

Interesting are the results of studying the blood parameters before treatment, depending on the biological subtype of the tumor in patients with subsequent progression for 6-12 months (Table 1).

First of all, it should be noted that this group included only breast cancer patients with luminal B and TNBC. It was found that in the blood of patients with luminal B before the start of chemotherapy, all the studied indicators had significant differences from the standard values of healthy donors. Thus, the level of TGF-β and its receptor TGF-βR2 was on average 1.9 times higher than the values in the blood of donors. The content of TNF-α and its TNF-αR1 and TNF-αR2 receptors before the start of treatment was increased by 4.3 times, 1.2 times and 1.8 times, respectively. The level of CD44 and MMR9 in the blood of patients with luminal BC during this period of the

Table 1. Growth and progression factors in the blood of breast cancer patients with subsequent progression for 6-12 months

Indicators	Donor	Luminal B		TNBC	
		Before therapy	After chemo	Before therapy	After chemo
TGFβ pg/ml	210.1±19.6	392.9±34.3[1]	331.7±31.5[1]	194.1±18.3	178.9±16.9
TGFβ-R2 pg/ml	99.7±8.2	194.3±17.5[1]	316±28.2[1,2]	255.1±26.1[1]	479.2±43.8[1,2]
TNF-α pg/ml	1.1±0.2	4.7±0.5[1]	5.9±0.5[1,2]	8.5±0.8[1]	8.5±0.9[1]
TNF-α-R1 pg/ml	405.2±35.4	486.6±42.3[1]	747.3±59.4[1,2]	755.4±63.1[1]	773.3±72.5[1]
TNF-α-R2 pg/ml	829.2±74.6	1471±112.8[1]	2309.6±256.7[1,2]	2757.7±242.1[1]	2442.3±252.3[1]
CD44 ng/ml	25.1±2.6	69.6±6.4[1]	94.7±8.3[1,2]	182.8±17.6[1]	181.5±19.4[1]
MMR9 ng/ml	48.3±4.6	181.6±17.9[1]	243.2±21.5[1,2]	162.4±14.2[1]	237.5±24.2[1,2]

Note: [1] – reliable in relation to the indicators of donors; [2] – reliable in relation to the "before treatment" stage ($p\leq0.05$).

study exceeded the normative indicators by 2.8 times and 3.8 times, respectively. In the blood of TNBC patients with subsequent progression, the content of TGFβ unexpectedly turned out to be at the level of values in donors, and the level of its TGF-βR2 receptor was increased by 2.6 times. The content of TNF-α and its TNF-αR1 and TNF-αR2 receptors before the start of treatment was increased by 7.7 times, 1.9 times and 3.3 times, respectively. The level of CD44 and MMR9 in the blood of patients was increased by 7.3 times and 3.4 times, respectively.

Analyzing the dynamics of changes in indicators after chemotherapy in the blood of patients with subsequent progression, it was revealed (Table. 1), the absence of significant changes in the level of TGF-β relative to the indicator before treatment. The TGF-βR2 receptor, on the contrary, increased in luminal BC by 1.6 times relative to the indicator before treatment and became 3.2 times higher than the norm; in TNBC, the increase compared to the indicators before treatment was 1.9 times and, accordingly, the indicator was 4.8 times higher than the normative values.

After neoadjuvant courses of chemotherapy, the level of CD44 in luminal BC increased by 1.4 times and became 3.8 times higher than normal, with TNBC-remained unchanged. The level of TNF-α during this period of the study in luminal BC increased by 25.5 % relative to the values before treatment and 5.4 times exceeded the normative indicators, while in TNBC it remained unchanged. TNF-αR1 and TNF-αR2 in the luminal subtype increased by 1.5 times and 1.6 times and became 1.8 times and 2.8 times higher than normal, respectively. In both studied types of breast cancer, the content of MMR9 in the blood of this contingent of patients increased: in luminal B – by 1.3 times, in TNBC – by 1.5 times, and in both cases, the indicators became higher than normal on average up to 5 times.

It was also of interest to consider the studied indicators before treatment, depending on the biological subtype of the tumor in patients with subsequent remission for at least 3 years. The results are presented in Table 2. It was found that in the blood of patients, almost all the studied indicators had significant differences from the standard values in the direction of increase. The exception was the level of TGF-β in patients with luminal A breast cancer, which did not significantly differ from healthy donors. With luminal B and TNBC, this indicator exceeded the standard values by 34.8 % and 73.4 %, respectively. The level of the TGF-βR2 receptor was also higher than normal in all biological subtypes of breast cancer – on average 4.4 times in luminal A and B, 6.3 times in TNBC. This was accompanied by an increase in the CD44 index by 1.8 times, 3.3 times and 7.3 times, respectively, with luminal A, luminal B

Table 2. Growth and progression factors in the blood of breast cancer patients with subsequent remission for 3 years

Indicators	Donors	Luminal A		Luminal B		TNBC	
		Before therapy	After chemo	Before therapy	After chemo	Before therapy	After chemo
TGFβ pg/ml	210.1±19.6	234.4±21.8	201.7±10.3[2]	283.3±29.2[1]	210.3±18.5[2]	364.3±33.1[1]	209.2±19.7[2]
TGFβ-R2 pg/ml	99.7±8.2	441.5±32.9[1]	191.1±17.5[1,2]	435.6±38.3[1]	200.8±19.4[1,2]	628.5±64.6[1]	207.1±22.4[1,2]
TNF-α pg/ml	1.1±0.2	4.2±0.4[1]	3.1±0.3[1,2]	8.7±0.9[1]	4.5±0.5[1,2]	6.3±0.6[1]	3.1±0.3[1,2]
TNF-α-R1 pg/ml	405.2±35.4	930.6±87.2[1]	445.2±46.9[2]	979.4±95.3[1]	595.2±51.6[1,2]	1067.8±89.1[1]	530.3±57.3[1,2]
TNF-α-R2 pg/ml	829.2±74.6	1557.7±132.9[1]	1064.2±96.4[1,2]	2404.4±156.3[1]	1616.1±142.7[1,2]	3508.8±253.1[1]	2036.95±189.2[1,2]
CD44 ng/ml	25.1±2.6	45.6±4.3[1]	34.1±3.2[1,2]	83.9±7.5[1]	58.7±6.0[1,2]	182.5±16.9[1]	82.7±7.5[1,2]
MMR9 ng/ml	48.3±4.6	136.9±11.3[1]	88.6±7.9[1,2]	181.9±14.2[1]	122.5±11.5[1,2]	196.5±17.3[1]	111.5±9.6[1,2]

Note: [1] – reliable in relation to the indicators of donors; [2] – reliable in relation to the "before treatment" stage ($p \leq 0.05$).

and TNBC. Assessing the levels of TNF-α and its TNF-αR1, TNF-αR2 receptors in each subtype of cancer, the following was obtained: with luminal A, an increase of 3.8 times, 2.3 times and 1.9 times, respectively; with luminal B – by 7.9 times, 2.4 times and 2.9 times, respectively; with TNBC – by 5.7 times, 2.6 times and 4.2 times. Also, a significant increase in the level of MMR9 relative to donors was observed in various biological subtypes of breast cancer – 2.8 times in luminal A, 3.8 times in luminal B, 4.1 times in TNBC.

The dynamics of changes in indicators after chemotherapy in the blood of patients with subsequent remission for at least 3 years is clearly shown in Table 2. During this period, the level of TGF-β and its receptor TGF-βR2 decreased relative to the previous period by 14 %, 25.8 %, 42.6 % and 56.7 %, 53.9 %, 67 %, respectively, in luminal A, luminal B and TNBC, respectively.

The dynamics of a decrease in the blood content of breast cancer patients was also noted for other studied indicators after chemotherapy. Thus, the level of CD44 decreased by 25.2 %, 30 % and 54.7 %, respectively, with luminal A, luminal B and TNBC; the level of TNF-α – by 26.2 %, 48.3 % and 50.8 %, respectively; TNF-αR1– by 52.1 %, 39.2 % and 50.3 %, respectively; TNF-αR2 – by 31.7 %, 32.8 % and 41.9 %, respectively; MMR9 – 35.3 %, 32.6 % and 43.3 %, respectively.

Our results are confirmed by the data of literary sources. CD44 is known to serve as a docking molecule for matrix metalloproteases (MMPs), which are matrix-modifying enzymes that destroy the basement membrane and promote cell migration [12]. MMR9, in turn, cleaves TGFβ for activation, which promotes angiogenesis and invasion [13]. According to the results of the study, Kuo Y. C. showed that TGFβ induces the expression of membrane-type MMP in breast cancer cells, which causes CD44 cleavage [14]. The cleaved CD44 then promoted the migration of tumor cells, which indicates a significant role of the CD44-MMP-TGF-β axis in cancer invasion and metastasis. CD44 also contributes to the emergence of multidrug resistance [15].

CONCLUSION

Thus, a complex of growth and progression factors has been identified that determines sensitivity and resistance to chemotherapy. A decrease in the level of TGF-β, TNF-α, MMR9 and CD44 after neoadjuvant chemotherapy determines further remission. On the contrary, the stabilization or increase in these indicators leads to an early progression of the malignant process in the period from 6 to 12 months. The assessment of indicators of growth factors and progression can play an important prognostic role with the help of which it is possible to distinguish a group of patients with the development of resistance to chemotherapy.

Authors contribution:
Franciyants E.M. – research concept and design, scientific editing, data analysis and interpretation.
Samaneva N.Yu. – data collection, analysis and interpretation, text writing, material processing, bibliography design, article preparation.
Vladimirova L.Yu. – research concept and design, scientific editing, data analysis and interpretation.
Storozhakova A.E. – research concept and design, scientific editing, data analysis and interpretation.
Kalabanova E.A. – technical editing.
Kabanov S.N. – design of the bibliography.
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