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CIRCULATING MIRNAS AS PREDICTIVE MARKERS FOR LINE I AND II NEOADJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER

Background. miRNAs have emerged as promising biomarkers for breast cancer, particularly in predicting treatment response and prognosis. Their ability to regulate gene expression and their presence in various bodily fluids make them valuable tools for personalized medicine. **Materials and Methods.** The study was based on a retrospective analysis of the results of the examination, treatment, and survival of 94 patients with stage II—III triple-negative breast cancer (TNBC) who underwent treatment at the Kyiv City Clinical Oncology Center during 2013—2017. miRNA expressions in blood serum were estimated using the real-time RT-PCR. **Results.** The elevated levels of miR-21, -155, -199a, and -200b ($p < 0.05$) were linked to metastasis to regional lymph nodes, while miR-373 and -126 expression levels were associated with the tumor stage (r = 0.55 and 0.57, respectively, $p < 0.05$). The higher serum levels of miR-21 (> 5.4, $p < 0.05$), -125b (> 6.0, $p < 0.05$) and the lower miR-205 levels (< 2.0, $p < 0.05$) were associated with the poorer response to line I and II neoadjuvant chemotherapy. The serum levels of miR-21, -125b, -126, -199a, -200b, -205, and -373 were found to correlate with the overall and recurrence-free survivals in TNBC patients. **Conclusions.** These findings suggest that miRNA-based biomarkers may have the potential as prognostic and predictive tools in TNBC, aiding in personalized treatment strategies.

Keywords: miRNA, triple-negative breast cancer, drug resistance.

An important factor that determines the successful treatment of breast cancer (BC) is the extent of cancer progression at the time of diagnosis. However, at least 50% of BC patients already have an invasive local tumor growth or metastases in distant organs at their first visit to the doctor. In this regard, an urgent problem is the development of methods for early BC detection that will allow for timely treatment of the disease [1].

The development of molecular biology has significantly widened the number of approaches for diagnosis, monitoring, and prediction of the BC course [2]. In particular, molecular and genomic approaches are used for genotyping solid tumors in cases where standard methods of cancer diagnosis have proven ineffective. However, despite high informativeness, they have certain limitations since tumor tissue cannot be used to monitor cancer devel-

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opment and evaluate the effectiveness of treatment, and, importantly, changes in tumor characteristics during treatment are not taken into account. The solution to these shortcomings is the use of circulating markers [3]. In recent years, numerous fundamental and clinical studies have established that circulating miRNA levels could serve as informative prognostic parameters in cancer patients.

The therapy of BC includes several regimens including neoadjuvant and adjuvant. In addition, in hormone receptor-positive BC cases, hormonal treatment is used. Combinations of anthracyclines such as doxorubicin, daunomycin, and epirubicin with taxanes such as paclitaxel and docetaxel are among the most common treatment strategies for advanced BC. Among neoadjuvant regimens, combinations of paclitaxel, docetaxel, doxorubicin, epirubicin, cyclophosphamide, and fluorouracil are most often used. A new trend in cancer treatment involves developing minimally invasive methods to predict the disease progression. This approach focuses on analyzing biological fluids, especially blood, without the need to take biopsies [4].

Triple-negative breast cancer (TNBC) is a particularly aggressive BC subtype with a poor prognosis. Unlike other BC subtypes, TNBC does not express hormone receptors (estrogen receptor, progesterone receptor, and HER2), limiting treatment options. The lack of targetable receptors makes TNBC more difficult to treat, leading to higher rates of recurrence and metastasis [5].

TNBC often presents at an advanced stage, with larger tumors and lymph node involvement, further complicating treatment and reducing survival rates. Additionally, TNBC patients are more likely to experience early recurrence and distant metastasis compared to other breast cancer subtypes. This aggressive behavior highlights the urgent need for novel therapeutic strategies and predictive biomarkers to improve the outcomes [5].

The development of novel predictive markers for TNBC is crucial for identifying patients who will benefit from neoadjuvant therapy. These markers can help guide treatment decisions, allowing for more personalized and effective therapies.

miRNAs are small non-coding RNA molecules approximately 22 nucleotides long that regulate gene expression by targeting specific regions of mRNA. Aberrant miRNA expression profiles contribute to cancer development and progression by modulating the activity of oncogenes and tumor suppressors. Changes in miRNA expression can be caused by genetic alterations, epigenetic modifications, or disruptions in transcriptional regulation [6].

Cancer cells exhibit abnormal miRNA expression patterns compared to normal cells. Oncogenic miRNAs promote tumor growth, invasion, and angiogenesis, while tumor-suppressive miRNAs inhibit these processes. The specific miRNA profile of a tumor can vary depending on the tissue of origin and can serve as a biomarker for early diagnosis and prognosis [6].

Circulating miRNAs that are found in body fluids are stable and can be detected using routine laboratory methods. Changes in the levels of circulating miRNAs have been linked to various cancer types, suggesting their potential as minimally invasive biomarkers for cancer diagnosis and monitoring [7].

Studies have shown that specific miRNAs play a significant role in determining how breast cancer responds to chemotherapy. When certain miRNAs, such as miR-451, miR-145, and others, are disrupted, cancer cells become more resistant to anthracyclines [8]. Several miRNAs have been identified as potential predictive markers in TNBC. For instance, overexpression of miR-21 as well as downregulation of miR-205 are associated with poor prognosis and increased tumor aggressiveness. Additionally, miR-155 and miR-146a have been implicated in the development and progression of TNBC, although their roles can be context-dependent [9].

Moreover, the levels of miRNAs in blood can be used as biomarkers to predict a patient's response to chemotherapy. For instance, high levels of miR-221 are linked to poor response, while elevated miR-4530 levels are associated with better responses [10—12]. Qattan et al. [13] have identified a panel of the circulating miR-93, miR-210, miR-19a, and miR-19b that can accurately predict a patient's likelihood of benefiting from specific chemotherapy regimens. García-Vazquez et al. [14] found that the expression levels of the circulating miR-30a, miR-9-3p, miR-770, and miR-143-5p are associated with the clinical response to neoadjuvant chemotherapy (NACT) in patients with TNBC.

While miRNAs hold significant promise as predictive markers for TNBC, several challenges remain. The standardization of miRNA detection methods, validation in large-scale clinical studies,

and identification of miRNA-based therapeutic targets are crucial for their clinical application. By addressing these challenges and continuing research efforts, miRNAs have the potential to revolutionize the diagnosis and treatment of TNBC.

We aimed to study the relationship between circulating miRNA expression and sensitivity to NACT in patients with TNBC and evaluate the possibilities of their use as predictive markers of treatment effectiveness.

Materials and Methods

We have conducted a retrospective analysis of the results of the examination, treatment, and survival of 94 patients with stage II—III TNBC who underwent treatment at the Kyiv City Clinical Oncology Center during 2013—2017. All subjects provided informed consent on the use of their clinical data for scientific purposes, and the research was approved by the Medical Ethical Committee of the Kyiv City Clinical Oncology Center and was carried out in conformity with the guidelines of the Declaration of Helsinki.

Table 1. **General clinical characteristics of BC patients**

Characteristics	Number of cases	
	N	%
Total number of patients	94	100
Age (years)		
Mean	56.1 ± 5.4	
Range	24—81	
Menstrual function		
Active menstrual cycle	41	43.62
Menopause	53	56.38
Stage		
II	57	60.64
III	37	39.36
Lymph node metastasis (TMN)		
N0	36	38.30
N1-N3	58	61.70
Histological type		
Infiltrative duct cancer	65	69.15
Infiltrative lobular cancer	29	30.85
Grade		
G1	22	23.40
G2	42	44.68
G3	30	31.91

The stage of cancer was determined according to the international tumor classification (TNM, 8th edition (2017)). All patients underwent the general clinical, biochemical, and laboratory tests, ultrasound of the abdomen, mammography, X-rays of the chest cavity, and puncture biopsy of tumors by the standards of diagnosis and treatment of cancer patients, approved by the Ministry of Health of Ukraine No. 140 dated 27.07.1998, No. 554 dated 17.09.2007, and No. 645 dated 30.07. 2010.

Depending on the clinical indications, all patients with stages II—III underwent organ-saving surgery or radical mastectomy by Madden and NACT by the standards of treatment approved in Ukraine. The courses include 2—6 cycles of the AP scheme (doxorubicin + paclitaxel/epirubicin + docetaxel) or the cisplatin/carboplatin scheme, with an interval of 21 days. NACT efficacy was evaluated every 2 cycles by mammography according to RECIST 1.1. criteria.

General clinical characteristics of patients and the results of the morphological and immunohistochemical study of tumors are presented in Table 1.

Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). miRNA expression was estimated in blood serum from BC patients. Samples of blood were collected following the patient's diagnosis before treatment. Blood was contained in K3 EDTA vials and centrifuged to isolate serum, which was stored at –20 °C. Total RNA from the serum samples was isolated using a commercial miRNeasy Serum/Plasma Kit (QIAGEN, Germany) according to the manufacturer's recommendations. The amount of isolated RNA was determined by spectrophotometry using a NanoDrop 2000c Spectrophotometer (Thermo Scientific, USA). The purity of the isolated RNA was monitored by the ratio of absorption values at wavelengths of 260 and 280 nm. RNA was dissolved in Tris-EDTA buffer and stored at –20 °C until use. The RT-PCR was performed using a quantitative detection system QuantStudio 5 Dx Real-Time PCR System (Thermo Fisher Scientific, USA) and a commercial kit for RT-PCR TaqMan MicroRNA Assay (Thermo Fisher Scientific, USA) according to the manufacturer's protocol.

The primer sequences for the detection of miRNAs were obtained using the resource ge-

nomics.dote.hu:8080/mirnadesigntool (Table 2) and synthesized by Metabion, Germany.

RNU48 miRNA was used as an endogenous control to objectify expression parameters (forward 5′-AGTGATGAT-GACCCCAGGTAACTC-3′ and reverse 5′-CTGC-GGTGATGGCATCAG-3′) [9]. The relative expression of miRNAs was determined by the comparative ΔCT method. The threshold cycle was averaged in all technical and biological replicas in the middle of each line. The fold change in the expression of the studied miRNAs was calculated by the formula $2^{-\Delta Ct}$. The errors of the fold change calculations show a range of ΔCt values based on the inclusion of the standard deviation in these values.

Statistical methods. Statistical processing of the obtained results was carried out using STATISTICA 6.0 program (Statistica Inc., USA). Standard descriptive, parametric, and non-parametric statistical methods were used. Testing of the statistical hypothesis about the normality of the distribution was carried out using Student's *t*-test (for a parametric distribution) or a Mann — Whitney U-test (for a non-parametric distribution). A recurrence-free survival analysis was carried out by the Mantel — Cox test. Differences at $p \leq 0.05$ were considered significant.

Results and Discussion

The selection of miRNAs for this research was based on the data on their involvement in the regulation of genes associated with cancer emergence and progression and the development of drug resistance. For this, using the tools of the resource ncbi.nlm.nih.gov (ProSplign, BLAST, GemBank, etc.) and http://www.mir2disease.org/, a panel of miRNAs was selected in several stages:

- Stage 1: selecting miRNAs involved in breast carcinogenesis (the resource http://www.mir2disease.org formed a list of 263 miRNAs for which a connection with oncogenesis in mammary gland has been experimentally proven).
- Stage 2: reducing the list of miRNAs according to the following characteristics: participation in the regulation of apoptosis, regulation of the expression of xenobiotic metabolism genes, and proven clinical significance. This search was based on the search for literature and clinical trials, patents, etc., as well as those miRNAs based on which anticancer drugs will be developed. As a result, we formed a list of 40 miRNA candidates.
- Stage 3: analyzing the sequences of the selected miRNAs using the resource ncbi.nlm.nih.

Table 2. **Primer sequences to determine the miRNAs expression**

miRNA ID	Stem-loop primer for cDNA synthesis	Forward primer
miR-125b	5′ – GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC GCCAAC – 3′	5′ – GTTTACCAGA CTTTTCCTAGTC – 3′
miR-126	5′ – GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC AGTAAT – 3′	5′ – GGGTCGTACC GTGAGTAAT – 3′
miR-155	5′ – GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC TCGTGA – 3′	5′ – GTGGGTTAA TGCTAATCGTGAT – 3′
miR-182	5′ – GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC TAGAAC – 3′	5′ – GTTGTTTGG CAATGGTAGAACT – 3′
miR-199a	5′ – GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC GCACAT – 3′	5′ – GGGACAGTA GTCTGCACAT – 3′
miR-200b	5′ - GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC TCATCA - 3′	5′ – GTTTGGTAA TACTGCCTGGTAA – 3′′
miR-205	5′ – GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC GTGGCC – 3′	5′ – GTTTCCTTCA TTCCACCGG – 3′
miR-21	5′– GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC TCAACA-3′	5′ – GTTTGGTAG CTTATCAGACTGA – 3′
miR-373	5′ – GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC TAAAAC – 3′	5′ – GTTTGGAAGT GCTTCGATTTTG – 3′
miR-375	5′ – GTTGGCTCT GGTGCAGGGT CCGAGGTATTC GCACCAGAGCCAAC TAACGA – 3′	5′ – GTTTGTTTGTCAA GAGCAATAACGAA – 3′

Table 3. **Relationship between the expression of serum miRNAs and the clinical and morphological features of TNBC, fold change**

miRNA	Stage		Metastases in regional lymph nodes		Differentiation grade			Histological type	
	II	III	N0	N1—3	G1	G2	G3	Ductal cancer	Lobular cancer
miR-21	5.2 ± 0.67	6.9 ± 1.5	5.2 ± 1.21	**7.5 ± 0.61** ⋆	5.7 ± 1.82	6.5 ± 1.59	6.1 ± 1.19	5.74 ± 1.57	6.2 ± 1.61
miR-155	4.9 ± 0.26	4.53 ± 0.46	3.8 ± 0.21	**5.2 ± 0.32** ⋆	4.5 ± 0.38	4.9 ± 0.39	5.0 ± 0.13	4.41 ± 0.28	4.33 ± 0.28
miR-182	3.9 ± 1.78	5.8 ± 1.55	3.9 ± 1.08	5.9 ± 1.09	3.9 ± 1.31	4.6 ± 1.41	5.3 ± 1.33	4.8 ± 2.11	4.7 ± 1.99
miR-373	7.6 ± 0.21	**9.3 ± 1.09** #	7.8 ± 0.5	**9.5 ± 1.08** ⋆	8.6 ± 1.09	8.5 ± 0.94	8.7 ± 1.20	8.13 ± 1.95	8.87 ± 2.21
miR-125b	6.72 ± 2.49	5.9 ± 2.92	4.6 ± 3.07	6.9 ± 2.83	5.7 ± 2.36	6.8 ± 2.69	7.2 ± 2.19	6.51 ± 2.22	6.33 ± 2.15
miR-126	3.7 ± 0.22	**4.8 ± 0.27** #	4.2 ± 0.47	4.3 ± 0.56	4.1 ± 0.51	4.6 ± 0.62	4.6 ± 0.37	4.1 ± 0.47	4.3 ± 0.52
miR-199a	0.62 ± 0.11	0.48 ± 0.35	0.79 ± 0.14	**0.45 ± 0.11** ⋆	0.58 ± 0.14	0.59 ± 0.14	0.61 ± 0.18	0.55 ± 0.2	0.62 ± 0.17
miR-200b	0.24 ± 0.05	0.21 ± 0.11	0.16 ± 0.04	0.28 ± 0.02 ⋆	0.17 ± 0.04	0.21 ± 0.12	0.15 ± 0.07	0.27 ± 0.05	0.22 ± 0.11
miR-205	2.5 ± 1.5	1.6 ± 1.39	1.6 ± 0.94	3.7 ± 0.99	2.2 ± 1.74	2.3 ± 1.19	1.6 ± 1.28	2.5 ± 1.32	2.6 ± 1.48
miR-375	0.64 ± 0.62	0.57 ± 0.42	0.67 ± 0.88	0.8 ± 0.49	0.79 ± 0.51	0.58 ± 0.37	0.42 ± 0.4	0.52 ± 0.28	0.63 ± 0.6

Notes: # $p < 0.05$, compared to the patients with II stage; ⋆ $p < 0.05$, compared to the N0 patients.

gov (BLAST TOOL) and determining their possible binding sites not only in the human genome but also in the available sequences of infectious disease pathogens (HBV, HPV, *Helicobacter pylori*, SARS-CoV-2, etc.) to identify possible overlaps of the sequences that reduce the prognostic value of miRNAs as markers of BC. When selecting miRNAs directly for research, we also took into account information on the frequency of SNP polymorphisms of their sequences. Finally, we formed a list of 10 miRNAs, namely miR-21, -miR-155, miR-182, miR-373, miR-125b, miR-126, miR-199a, miR-200b, miR-205, and miR-375.

- Stage 4: analysis of the expression of selected miRNAs in blood serum of 94 TNBC patients to estimate their predictive and prognostic utility.

We did not find any association of miR-155, -182, -125b, -205, and -375 with the cancer stage, metastasis in the regional lymph nodes, differentiation grade, and histological type of tumors. Along with this, the relationship between the expression indicators of oncogenic miRNA-373 and the stage of TNBC ($r = 0.55$, $p < 0.05$) and metastases in regional lymph nodes ($r = 0.57$, $p < 0.05$) was determined. The levels of tumor suppressor miR-126 in patients with stage II TNBC were 4.8 ± 0.27, which is significantly higher than in patients with stage II of BC ($p < 0.05$).

As shown in Table 3, the expression levels of miR-21, -155, -373, -199a, and -200b in patients with lymph node lesions were significantly different from those in patients without metastases. In patients with metastases, miR-21, -155, and -200b levels were 1.44, 1.39, and 1.75 times higher and miR-199a levels were 1.76 times lower than in the N0 cohort ($p < 0.05$).

To study the relationship between the expression of circulating miRNAs and sensitivity to NACT in patients with TNBC, we used clinical material from 94 patients who received combina-

Table 4. **Distribution of patients with TNBC by the clinical effect of NACT (according to the RECIST 1.1. criteria)**

NACT clinical effect	Line I (AP scheme)	Line II (cisplatin/carboplatin)
	n = 94	n = 43
Complete regression	18 (19.15%)	10 (23.26%)
Partial regression	33 (35.11%)	11 (25.58%)
Stabilization	22 (23.40%)	12 (27.91%)
Progression	21 (22.34%)	10 (23.26%)

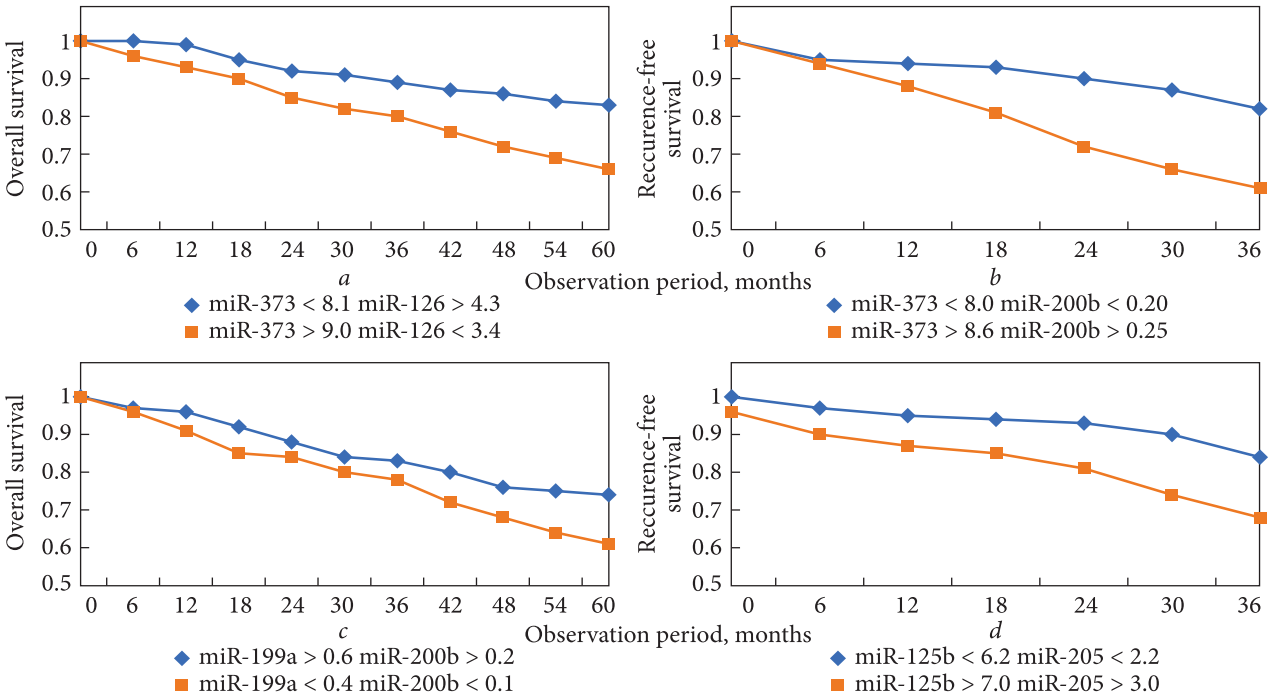

Fig. 1. Overall (*a*) and recurrence-free (*b*) survival of TNBC patients who received line I NACT and overall (*c*) and recurrence-free (*d*) survival of TNBC patients who received line II NACT depending on the circulating miRNAs levels

tions of doxorubicin + paclitaxel (46 patients) and epirubicin + docetaxel (48 patients) as line I therapy. Of these, 22 patients received cisplatin and 21 received carboplatin as line II drugs (Table 4). Depending on the severity of the clinical effect of NACT (according to RECIST criteria 1.1), the patients were divided into 2 groups. Group 1 included patients who had complete and partial cancer regression and were considered sensitive, while the cases with cancer stabilization and progression were considered resistant and distributed to group 2 (Table 4).

We also divided patients into 4 groups by median miRNA levels and estimated the association of high/low miRNA levels with the response to NACT: 12 patients demonstrated complete regression, 22 — partial regression, 15 — stabilization, and 14 — progression of tumor process (Table 5).

We found that the expression levels of circulating miR-125b and -205 in blood serum of patients with TNBC before the start of treatment of above 4.9 and below 2.8, respectively, are characteristic of cancer cases sensitive to the line 1 NACT regimens (combinations of anthracyclines with taxanes: doxorubicin, epirubicin, paclitaxel, docetaxel). The levels of miRNA-125b > 6.0 and miRNA-205 < 2.0 were determined in the serum of patients with resistant tumors (Table 5).

Table 5. **Distribution of patients with TNBC by the level of expression of circulating miRNAs depending on the clinical effect of chemotherapy, n/%**

miRNA level		Clinical assessment of NACT (RESIST criteria 1.1.)			
Line I		Complete regression n = 18	Partial regression n = 33	Stabilization n = 22	Progression n = 21
	miR-125b < 4.9 miR-205 > 2.8	16/88.9%	26/78.8%	5/22.7%	3/14.3%
	miR-125b > 6.0 miR-205 < 2.0	2/11.1%	7/21.2%	17/77.3%	18/85.7%
Line II		Complete regression n = 10	Partial regression n = 11	Stabilization n = 12	Progression n = 10
	miR-21 < 5.4	10/100%	10/81.8%	2/16.7%	1/10%
	miR-21 > 5.4	0	1/18.2%	10/83.3%	9/90%

We have revealed that the levels of circulating miR-182, -21 in TNBC patients who had already received treatment, predict the sensitivity of tumors to line II drugs, in particular, cisplatin and carboplatin. The levels of miRNA-21 < 5.4 and miRNA-182 < 4.0 indicate the sensitivity of neoplasms to platinum drugs, while indicators > 6.7 and > 6.0, respectively, indicate poor response ($p < 0.05$).

Considering the obtained data on the connection between the expression of miRNA-21, -155, -182, -373, -125b, -126, -199a, -200b, -205, -375 and the stage of TNBC, the presence of lymph node metastases, and drug sensitivity, we analyzed their association with overall and recurrence-free survivals of TNBC patients (Fig. 1).

We have established that the overall survival (OS) of patients who received line I therapy and exerted expression levels of miRNA-373 < 8.1 and miRNA-126 > 4.3 was 20 % higher compared to the patients with miRNA-373 levels > 9.0 and miRNA-126 levels < 3.4 (Fig.1, *a*).

The patients with expression of miR-373 < 8.0 and miR-200b < 0.20 had the best indicators of recurrence-free survival rate (RFS) compared to those with miR-373 expression > 8.6 and miR-200b levels < 0.25 ($p < 0.05$) (Fig.1, *b*).

Expression of miR-199a > 0.6 ($p < 0.05$) and miR-200b > 0.2 ($p < 0.05$) in TNBC patients who received line II therapy was associated with better survival rates (Fig.1, *c*). Patients with miR-125b > > 7.0 and miR-205 > 3.0 demonstrated twice lower RFS compared to patients with miR-125b < 6.2 and miR-205 < 2.2 ($p < 0.05$) (Fig.1, *d*).

To date, some prognostic and predictive miRNA panels have been developed for TNBC and are effectively used in clinical practice. In particular, more than 1,026 patents have been registered in the world regarding the use of miRNAs as markers of the sensitivity of BC to drug therapy. According to the literature and the results of experimental studies, disruption of the expression of miRNA-451, -145, -298, -200c, and -326 in BC cells causes the activation of the *MDR1* gene and contributes to a decrease in sensitivity to anthracyclines [16].

Zhao et al. [11] demonstrated that BC patients with high miR-221 levels in blood plasma show worse response to NACT with anthracyclines and taxanes. Wang et al. [12] showed that the elevated level of miR-4530 in the blood serum of BC patients indicated the high efficiency of NACT based on taxanes and anthracyclines. Other researchers found that assessment of levels of circulating miR-125b, miRNA-19a, and miRNA-205 allowed them to predict with high accuracy the response of BC to chemotherapy with anthracyclines and taxanes [17]. Shao et al. [18] proved that the use of a panel consisting of three miRNAs (miR-200a, -210, and -451) allows one to predict with high accuracy the sensitivity to taxanes and anthracyclines in patients with disseminated BC.

To summarize, our study has revealed a relationship between the serum levels of miR-373 and -126 and the stage of TNBC, and of miR-21, -155, -199a, and -200b and metastases in regional lymph nodes. Also, we have shown an association of serum miR-125b and -205 with the response to the line I NACT and miR-21 with the response to the line II NACT. We have established a relationship between the indicators of overall and recurrence-free survivals of patients and TNBC and the levels of circulating miR-21, -125b, -126, -199a, -200b, -205, and -373.

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ЦИРКУЛЮЮЧІ МІКРОРНК ЯК МАРКЕРИ ЧУТЛИВОСТІ ДО НЕОАД'ЮВАНТНОЇ ХІМІОТЕРАПІЇ І ТА ІІ ЛІНІЙ У ХВОРИХ НА ТРИЧІ НЕГАТИВНИЙ РАК МОЛОЧНОЇ ЗАЛОЗИ

Вступ. МікроРНК є багатообіцяючими біомаркерами раку молочної залози (РМЗ), особливо для прогнозування відповіді на лікування. Їхня здатність регулювати експресію генів і присутність у різних рідинах організму робить їх цінними інструментами для персоналізованої медицини. Оскільки дослідження їх просуваються, біомаркери на основі мікроРНК мають потенціал для революції в діагностиці та лікуванні РМЗ, що сприятиме покращенню результатів лікування пацієнтів. **Матеріали та методи**. Проведено ретроспективний аналіз результатів обстеження, лікування та виживаності 94 пацієнтів з II—III стадіями тричі-негативного РМЗ, які перебували на лікуванні в Київському міському клінічному онкологічному центрі впродовж 2013—2017 рр. Експресію мікроРНК в сироватці крові оцінювали за допомогою кількісної ПЛР у режимі реального часу. **Результати**. Підвищені рівні мікро РНК -21, -155, -199a і -200b (7,5 ± 0,61, 5,3 ± 0,32, 9,5 ± 1,08, 0,45 ± 0,11 і 0,28 ± 0,02, відповідно) були пов'язані з метастазами в регіонарні лімфатичні вузли, тоді як експресія мікроРНК-373 і -126 була асоційована зі стадією пухлинного процесу (r = 0,55 і 0,57 відповідно, $p < 0,05$). Вищі рівні мікроРНК-21 (> 5,4, $p < 0,05$), -125b (> 6,0, $p < 0,05$) і нижча експресія мікроРНК-205 (< 2,0, $p < 0,05$) у сироватці крові асоціювалися з гіршою відповіддю на неоад'ювантну хіміотерапію першої та другої ліній. Виявлено, що сироваткові рівні мікроРНК -21, -125b, -126, -199a, -200b, -205 і -373 корелюють із загальною та безрецидивною виживаністю в пацієнтів з тричі-негативним РМЗ. **Висновки**. Отримані результати свідчать про те, що мікроРНК мають потенціал як прогностичні та предиктивні інструменти для тричі-негативного РМЗ, допомагаючи підібрати персоналізовані стратегії лікування.

Ключові слова: мікроРНК, тричі негативний рак молочної залози, лікарська резистентність.