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EXPRESSION PATTERN OF MIR-125B-2, -155, -221, AND -320A IS ASSOCIATED WITH RESPONSE OF BREAST CANCER PATIENTS TO TAMOXIFEN

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***Background*: Hormonal therapy is one of the main methods of comprehensive treatment of patients with locally advanced breast cancer (BC). Despite the intensive search for molecules associated with the aggressiveness of the tumor process, currently there are no reliable markers predicting response to neoadjuvant hormonal therapy (NHT). *Aim:* To investigate the correlation between miR-125b-2, -155, -221, -320a expression in tumor tissue and HER2/neu status and response to tamoxifen treatment in BC patients. *Materials and Methods*: Expression levels of miR-125b-2, -155, -221, and -320a were analyzed in biopsy samples of 50 BC patients using a real-time polymerase chain reaction. *Results*: We found that levels of miR-125b-2, -155, -221, and -320a were 1.72, 1.65, 1.85, and 2.89 times higher in BC biopsy samples expressing estrogen/progesterone receptors and HER2/neu compared with HER2/neu-negative luminal tumors. Patients with a luminal BC showing higher levels of miR-125b-2 and miR-320a expression before therapy demonstrated better response to NHT with tamoxifen. A strong correlation was calculated for miR-221 expression and response to NHT (r = 0.61). *Conclusions*: The high levels of miR-125b-2, -155, -221, and -320a in tumor tissue are associated with the HER2/neu-positive status of luminal BC subtypes. Tumor samples of patients showing the low response to NHT with tamoxifen are characterized by lower expression of miR-125b-2 and -320a. Hence, miR-125b-2 and -320a could be considered as putative predictive biomarkers associated with tamoxifen sensitivity of hormone-dependent BC.**

***Key Words:* breast cancer, miRNA, tamoxifen, resistance.**

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The problem of drug resistance is an important issue of modern oncology. To date, tamoxifen is one of the most common hormonal drugs, prescribed to the patients with hormone-dependent breast cancer (BC). At the same time, there are only few other drugs that have proven efficiency for treatment of such cases due to the presence of the numerous cancer cell clones with different molecular profile within tumor, as well as acquisition of hormone-independent phenotype by cancer cells during treatment.

Neoadjuvant hormonal therapy (NHT) before surgical resection of tumors positively affects the disease-free survival rates in BC patients, and it is important to understand if the patient will benefit from such treatment regime [1].

miRNAs are short non-coding RNAs that affect gene expression at the post-transcriptional level. Their role in cancer development has been already proven, as well as their potential to become prognostic and predictive markers of different cancers including BC [2].

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Abbreviations used: BC – breast cancer; ER – estrogen receptor; NHT – neoadjuvant hormonal therapy; PR – progesterone receptor; qRT-PCR – real-time quantitative reverse transcription polymerase chain reaction.

After a detailed search using such resources ashttp://mircancer.ecu.edu,https://www.mirbase.org, https://www.oncomir.umn.edu/omcd, etc., as well as literature search, we chose miR-125b-2, -155, -221, -320a, because their expression is proven to be associated with hormone receptor presence and sensitivity to hormonal therapy. Most data on miRNA in BC were obtained in cell lines and there are a few experiments that were conducted on clinical material. For example, miR-221 is considered to be one of the most important players in the development on tamoxifen resistance since Miller *et al*. [3] reported its direct association with HER2/neu status and p27 as its direct target during tamoxifen resistance development by MCF-7 cells. Up-to-date, it has been shown that miR-221 is involved in hormone receptor (especially estrogen receptor) regulation, proliferation and overall aggressiveness of BC [4, 5]. More recent works are focused on the association of circulating miR-221 as prognostic and predictive marker, but it is still unclear how its levels in tumor tissue are associated with clinical and pathological cancer characteristics [6].

Thus, the aim of our research was to investigate the correlation between miR-125b-2, -155, -221, -320a expression in tumor tissue and HER2/neu status and response to tamoxifen treatment in BC patients.

MATERIALS AND METHODS

The study is based on a retrospective analysis of the treatment outcomes of 50 patients with locally disseminated hormone-dependent BC of stages II–III, who were treated on an outpatient basis at the Transcarpathian Antitumor Center during 2011–2020. All patients were examined using conventional clinical and laboratory methods according to the standards of diagnosis and treatment of cancer patients, approved by the order of the Ministry of Health of Ukraine (№ 140 of 27.07.1998; № 554 of 17.09.2007; № 645 of 30.07.2010; and № 396 of 30.06.2015) and gave informed consent on the use of their clinical data for scientific purposes. All samples were encoded and depersonalized.

All patients enrolled in the study received NHT, which included tamoxifen (20 mg/day as monotherapy, 2–4 cycles) or letrozole (2.5 mg/day, 2–4 cycles). The effectiveness of therapy was evaluated with each cycle (month) by mammography and ultrasound diagnosis of mammary glands according to RECIST 1.1 criteria [7].

All patients underwent surgical treatment (quadrant or lumpectomy with regional lymph dissection, radical mastectomy according to Maden). In the adjuvant mode, polychemotherapy was performed in patients with a high risk of progression, according to the schemes that are standardly used in BC patients: SMF, AC, TC (4–6 courses). After the operation, radiation therapy was performed on the postoperative scar, axillary, parasternal, and supraclavicular areas ("TERAGAM" device, single focal dose — 2 Gy, total focal dose — 42–44 Gy). Patients with positive expression of estrogen receptors in the removed tumor were prescribed prolonged hormonal therapy according to standard schemes (tamoxifen, aromatase inhibitors) depending on the individual clinical data.

Morphological and immunohistochemical studies were carried out in the Pathomorphology Department of the Transcarpathian Antitumor Center. The histological type of removed tumors was verified during morphological examination (hematoxylin and eosin staining).

Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). MiRNA expression was estimated in biopsy samples taken before NHT. The expression of miR-125b-2-5p, -155-3p, -221-3p, -320a-3p in tumor tissue was analyzed by qRT-PCR. Total RNA was extracted from formalin fixed paraffin embedded tumor samples using commercial "RNeasy FFPE Kit" (Qiagen, Germany). The quantity of isolated RNA was determined on a "NanoDrop 2000c" spectrophotometer (Thermo Fisher Scientific, USA). The purity of isolated RNA was controlled by measuring optical absorption at 260 and 280 nm. RNA was dissolved in Tris-EDTA buffer and stored at –20 °C. qPCR was performed on a QuantStudio 5 Dx Real-Time PCR System (Thermo Fisher Scientific, USA) with a commercial Luna Universal qPCR Master Mix PCR kit (New England Biolabs, USA) according to the manufacturer's protocol. To determine miRNA expression, we used a single stem-loop primer for synthesis of cDNA and universal reverse primer 5′-GTGCAGGGTCCGAGGT-3′, according to the methods of stem-loop miRNA RT-qPCR [8]. Sequences of primers were obtained via resource genomics.dote.hu:8080/mirnadesigntool/ and synthesized by Metabion, Germany (Table 1).

The expression of miRNAs was determined using the $2^{-\Delta CT}$ method relative to RNU48 miRNA used as a reference gene (endogenous control). Primer sequences were taken from www.ncbi.nlm.nih.gov and synthesized by Metabion, Germany: RT-primer: 5′-CTCTGACC-3′, forward 5′-AGTGATGATGACCCCAGGTAACTC-3′, reverse 5′-CTGCGGTGATGGCATCAG-3′. ΔCT (delta threshold cycle) values were calculated automatically by QuantStudio 5 Dx Real-Time PCR System (Thermo Fisher Scientific, USA) by following formula:

ΔCT = CT (a target gene) – CT (a reference gene).

All values of miRNA expression are presented as $2^{-\Delta CT}$.

Statistical methods. Statistical analysis of the obtained data was performed using the program STATISTICA 6.0. All data was expressed as the mean ± SD of at least 3 independent experiments. The differences between the groups were analyzed using the Student's *t*-test and ANOVA; $p < 0.05$ was considered significant. To determine the variation of the selected miRNA expression in samples among different groups, the data of miRNA expression obtained by qRT-PCR were analyzed by Pearson's correlation coefficient (r).

RESULTS AND DISCUSSION

The general clinical characteristics of BC patients are shown in Table 2. The $^4/_5$ patients were at menopause. By histological structure of tumors, infiltrative ductal carcinoma of moderate differentiation grade prevailed. A comprehensive examination of the patients conducted before the start of treatment revealed metastases (N1–3) in regional lymph nodes in the large majority of patients. In the study, only BC cases with positive expression of estrogen and progesterone hormone receptors were included, half of which has a positive HER2/neu status. Depending on the clinical effect of NHT (according to the RECIST criteria), the patients were divided into 2 subgroups: group 1 with positive

Table 1. Primer sequences for miRNAs used in the study

miRNA	Stem-loop primer	Forward primer
hsa-miR-125b-2-5p	5′- GTTGGCTCTGGTGCAGGG TCCGAGGTATTCGCA CCAGAGCCAAC TCACAA -3′	5′- GTTTCCCTGAGACCCTAAC -3′
hsa-miR-155-3p	5′- GTTGGCTCTGGTGCAGGG TCCGAGGTATTCGCA CCAGAGCCAAC TGTTAA-3′	5′- GTGGGTTAATGCTAATCGTGAT -3′
hsa-miR-221-3p	5′- GTTGGCTCTGGTGCAGGG TCCGAGGTATTCGCA CCAGAGCCAAC GAAAC -3′	5′- GGAGCTACATTGTCTGCTG -3′
hsa-miR-320a-3p	5′- GTTGGCTCTGGTGCAGGG TCCGAGGTATTCGCA CCAGAGCCAAC TCGCCC -3′	5′- GGGAAAAGCTGGGTTGAGA -3′

Table 2. Clinical and pathological characteristics of patients with breast cancer

	Number of patients	
	n	%
Total number of patients	50	100
Average age, years	54.2 ± 3.9	
Age, range	46–79	
Menstrual function is preserved	10	20
Menopause	40	80
Stage		
II	33	66
III	17	34
Presence of metastases in regional lymph nodes		
N0	8	16
N1–N3	42	84
Histological type of neoplasm		
Infiltrative ductal cancer	36	72
Infiltrative lobular cancer	14	28
Differentiation grade		
G1 (high)	6	12
G2 (moderate)	38	76
G3 (low)	6	12
Expression of steroid hormone receptors		
ER+	50	100
PR+	50	100
HER2/neu+	25	50
HER2/neu-	25	50
Molecular subtype		
Luminal A	25	50
Luminal B	25	50

response to NHT and group 2 with tumors resistant to the treatment (Table 3).

Firstly, we have estimated miR-125b-2, -155, -221, and -320a expression levels in all BC patients depending on clinical and pathological features. We found no correlation between expression of these microRNAs and age, menstrual status, stage, regional lymph node metastases, histological type of tumor and its differentiation grade.

Then we compared the groups of patients with different HER2/neu status and, therefore, different molecular BC subtypes, and found that in the HER2/neu$^+$ (luminal B) group, the expression levels of all studied microRNAs were higher than in HER2/neu$^-$ (luminal A) tumors (Fig. 1, Table 4). In HER2/neu$^+$ tumors expression levels of miR-125b-2, -155, -221, and -320a were by 1.72, 1.65, 1.85, and 2.89 times higher than in the HER2/neu$^-$ tumors.

Interestingly, a similar association of miR-125b expression with HER2/neu status was established by Sui *et al*. [9] in gastric cancer.

Luo *et al.* [10] reported that high miR-125b expression significantly correlated with tumor size and TNM stage in HER2/neu-positive BC, along with a poor prognosis. At the same time, they found that most HER2/neu-positive cases had higher levels of miR-125b.

Lu *et al*. [11] reported that expression levels of miR-155 inversely correlated with estrogen receptor (ER) and progesterone receptor (PR) expression while no correlation with HER2/neu was evident. This controversy with our data can be assigned to the differences of BC sampling mostly composed from HER2/neu$^+$ tumors. Song *et al.* [12] demonstrated that upregulated miR-155 levels are observed in HER2/neu positive BC cases of advanced TNM stage, with lymph node metastasis, and vascular invasion.

Many authors claim miR-221 association with HER2/neu presence, as well as a molecular BC subtype, however, most of the studies were conducted *in vitro* [13–15].

For miR-320a, we also found some controversy between our results and other authors. Yang *et al.* [16] stated that they found no significant differences between the expression levels of miR-320a and ER, PR, and HER2/neu status. Nevertheless, in the Ukrainian

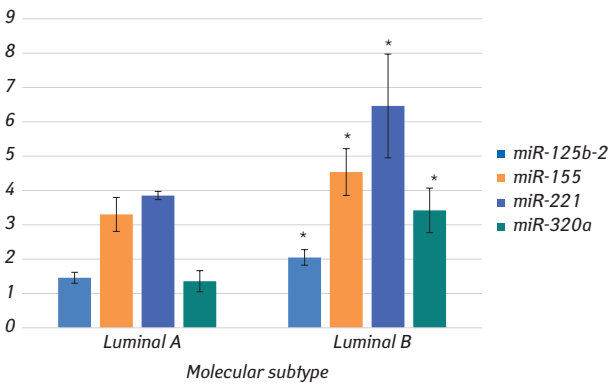

Fig. 1. Expression of miR-125b-2, -155, -221, and -320a 3p in luminal A and B BC samples. *The difference is significant compared to luminal A subtype, $p \leqslant 0.05$

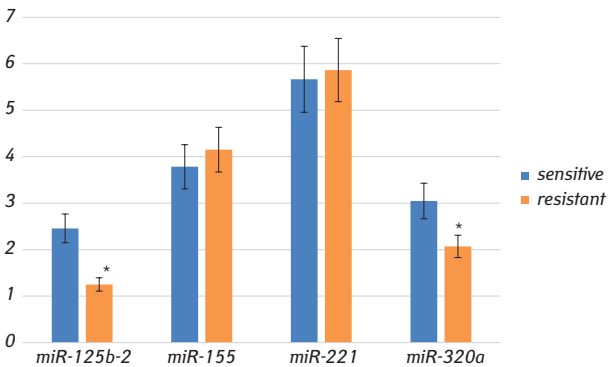

Fig. 2. Expression of miR-125b-2, -155, -221, and -320a 3p in BC samples depending on response to tamoxifen treatment. *The difference is significant compared to tamoxifen-sensitive group, $p \leqslant 0.05$

Table 3. The clinical effect of NHT (according to RECIST 1.1. criteria)

	Number of patients, n (%)			
	Sensitive		Resistant	
	Full regression	Partial regression	Stabilization	Progression
Tamoxifen (n = 50)	0	30 (60.0)	14 (28.0)	6 (12.0)

Table 4. Expression of miR-125b-2-5p, -155, -221-3p, and -320a-3p depending on HER2/neu status of luminal BC, mean ± SD

	miR-125b-2	miR-155	miR-221	miR-320a
ER$^+$PR$^+$HER2/neu$^+$	2.05 ± 0.12	4.53 ± 1.51	6.45 ± 0.96	3.42 ± 0.13
ER$^+$PR$^+$HER2/neu$^-$	1.19 ± 0.31*	2.75 ± 0.65*	3.48 ± 0.42*	1.18 ± 0.33*

Note: *$p \leqslant 0.05$ compared to ER$^+$PR$^+$HER2/neu$^+$ BC

population, Lukianova *et al*. [17] reported that HER2/neu$^+$ BC samples showed higher miR-320a expression than the triple negative BC.

Finally, we have analyzed the miRNAs expression depending on the response to tamoxifen (Table 2). We found that sensitive tumors are characterized by higher levels of miR-125b-2 and miR-320a (2.3 and 1.68 times, respectively, $p < 0.05$) (Fig. 2). At the same time, we observed a strong correlation of miR-221 with RECIST percentage (r = 0.61), however, significant differences between sensitive and resistant groups were not established.

miR-125b is known to be involved in the acquisition of resistance to the wide spectrum of anticancer drugs, such as aromatase inhibitors, paclitaxel, doxorubicin, etc. [18, 19]. Only a few authors report its association with tamoxifen response. Kim *et al.* [20] examined miR-125b validity as BC marker predictive for tamoxifen sensitivity on the sample that included only luminal BC cases with different HER2/neu status. The authors reported that higher miR-125b expression in BC tissue of patients undergoing tamoxifen treatment is associated with poor relapse-free survival rates, but there were no available data on association of miR-125b expression with NHT outcome.

The study [21] showed miR-155 ability to mediate tamoxifen resistance in BC, but in our work, we found no significant differences in its expression between the groups sensitive and resistant to tamoxifen (Fig. 2).

The data on miR-221 association with tumor response to tamoxifen treatment diverge from the results obtained on cell lines, where authors established a negative association of its expression with tamoxifen sensitivity. Particularly, Ouyang *et al.* [22] showed that miR-221/222 sponge abrogates tamoxifen resistance by restoring ER expression in MCF-7 cells.

Downregulation of miR-221/222 enhances the sensitivity of BC cells to tamoxifen through upregulation of tissue inhibitor of metalloproteinase-3 [23], and is involved in regulation of other elements of tumor stroma (matrix metalloproteinases, cytokine signaling, etc.) [24]. Ravegnini *et al.* [25] performed a meta-analysis of prognostic role of miR-221 expression in cancer patients and found a lot of controversy in the results of different studies.

There is a single report about the role of miR-320a in tamoxifen resistance in BC showing that sensitive tumors possess higher levels of its expression compared to resistant ones [26].

To sum up, the obtained results allow us to conclude that high levels of miR-125b-2, -155, -221, and -320a in tumor tissue are associated with HER2/neu-positive status of luminal BC subtypes. Tumor samples of patients showing the low response to NHT with tamoxifen are characterized by lower expression of miR-125b-2 and -320a. Hence, miR-125b-2 and -320a could be considered as putative predictive biomarkers of tamoxifen sensitivity of hormone-dependent BC.

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АСОЦІАЦІЯ ЕКСПРЕСІЇ мікроРНК-125B-2, -155, -221, -320A З ЧУТЛИВІСТЮ ПУХЛИН МОЛОЧНОЇ ЗАЛОЗИ ДО ТАМОКСИФЕНУ

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Гормональна терапія є одним з основних методів комплексного лікування хворих на місцево-поширений рак молочної залози (РМЗ). Незважаючи на інтенсивність досліджень, присвячених пошуку маркерів, пов'язаних з агресивністю пухлинного процесу, на сьогодні немає достовірних маркерів, що передбачають відповідь хворих на неоад'ювантну гормональну терапію у зв'язку з високою внутрішньопухлинною гетерогенністю РМЗ. ***Мета***: дослідити прогностичну роль мікроРНК-125b-2, -155, -221, -320a в пухлинній тканині хворих на гормонозалежний РМЗ до початку неоад'ювантної гормональної терапії (НГТ). ***Матеріали та методи***. Рівні експресії мікроРНК-125b-2, -155, -221, -320a у біопсійних зразках 50 пацієнток з РМЗ визначали за допомогою полімеразної ланцюгової реакції в реальному часі. ***Результати***: Встановлено, що рівні мікроРНК-125b-2, -155, -221 та -320a в 1,72, 1,65, 1,85 і 2,89 раза є вищими в зразках біопсії РМЗ, позитивних за експресією рецепторів естрогену, прогестерону та HER2/neu. У хворих на РМЗ з вищими рівнями експресії мікроРНК-125b-2 і мікроРНК-320a до лікування спостерігали кращу відповідь на неоад'ювантну терапію тамоксифеном. Встановлено пряму кореляцію рівнів мікроРНК-221 з відповіддю на лікування тамоксифеном за критеріями RECIST (r = 0,61). ***Висновки***. Показано, що високі рівні miR-125b-2, -155, -221, -320a в пухлинній тканині пов'язані з HER2/neu-позитивним статусом люмінального РМЗ. У хворих з гіршою відповіддю на терапію тамоксифеном спостерігалися низькі показники мікроРНК-125b-2 і -320a в біопсійних зразках. Таким чином, досліджувані мікроРНК потенційно можуть використовуватися в якості предиктивних біомаркерів, асоційованих з чутливістю гормонозалежного РМЗ до тамоксифену.

***Ключові слова*:** рак молочної залози, мікроРНК, тамоксифен, резистентність.