УДК 616.89-008.19-055.2-053.8/.9
https://doi.org: 10.20538/1682-0363-2020-1-13–20

The role of epidermal growth factor receptor (EGFR) in the efficacy of neoadjuvant chemotherapy in triple-negative breast cancer patients

Babyshkina N.N.[1, 2], Dronova T.A.[1, 2], Zambalova E.A.[1], Zavyalova M.V.[1, 2, 3], Slonimskaya E.M.[1, 3], Cherdyntseva N.V.[1, 2]

[1] *Cancer Research Institute, Tomsk National Research Medical Center (NRMC) of Russian Academy of Sciences 5, Kooperativny Str., Tomsk, 634050, Russian Federation*

[2] *National Research Tomsk State University (NR TSU) 36, Lenin Av., Tomsk, 634050, Russian Federation*

[3] *Siberian State Medical University (SSMU) 2, Moscow Trakt, Tomsk, 634050, Russian Federation*

ABSTRACT

Background. Identification of predictive molecular markers of triple-negative breast cancer (TNBC) will enable the evaluation of the efficacy of neoadjuvant chemotherapy (NACT) and define optimum approaches for the prognosis of the disease course in TNBC patients.

The aim of the study was to examine the correlation between the expression of the epidermal growth factor receptor (EGFR), its gene's polymorphic variants and the neoadjuvant chemotherapy (NACT) efficacy in triple-negative breast cancer (TNBC) patients.

Materials and methods. The study included 70 patients with triple-negative breast cancer, who had received 2-4 cycles of FAC and CAX regimens. The efficacy of the neoadjuvant chemotherapy was assessed according to the RECIST scale. The EGFR expression level in tumors before and after the NACT was evaluated with the help of immunohistochemistry. Genotypes for E*GFR* (rs2227983 and rs1468727) were detected by a real-time PCR.

Results. It was found that NCT significantly decreases the EGFR expression level in the tumor ($p = 0.000$). The research associates the objective clinical response as well as the pathological complete response with the low EGFR expression level ($p = 0.007$ and $p = 0.000$ respectively). Patients carrying the *EGFR*CC mutant genotype of rs1468727 did not achieve a pathological complete response ($p = 0.042$). In addition, patients with *EGFR*CC mutant genotype are more likely to have tumors with a high EGFR expression compared to *EGFR*TT wild-type genotype patients ($p = 0.047$).

Conclusion. The EGFR expression level in tumor tissue and the polymorphic variants of its gene in the rs1468727 locus can be considered as potential molecular markers with predictive significance in relation to the NACT efficacy in triple-negative breast cancer patients.

Key words: Triple-negative breast cancer, neoadjuvant chemotherapy, epidermal growth factor receptor (EGFR); gene polymorphisms.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Source of financing. The research was conducted under financial support from the Russian Science Foundation (RSF), Grant No. 19-75-30016 "New strategy for the prediction and prevention of distant metastasis based on the detection of circulating metastasis-initiating and niche-forming cells and their specific targets".

Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The research was carried out according to the principles of voluntariness and confidentiality in

✉ *Babyshkina Nataliya N.*, e-mail: nbabyshkina@mail.ru.

compliance with the "Fundamentals of the Legislation of the Russian Federation on the Protection of Public Health (Decree of the President of the Russian Federation of December 24, 1993 No. 2288) based on the permission of the local committee on biomedical ethics of the Cancer Research Institute, Tomsk National Research Medical Center.

For citation: Babyshkina N.N., Dronova T.A., Zambalova E.A., Zavyalova M.V., Slonimskaya E.M., Cherdyntseva N.V. The role of epidermal growth factor receptor (EGFR) in the efficacy of neoadjuvant chemotherapy in triple-negative breast cancer patients. *Bulletin of Siberian Medicine.* 2020; 19 (1): 13–20. https://doi.org: 10.20538/1682-0363-2020-1-13–20.

Роль рецептора эпидермального фактора роста EGFR в эффективности неоадъювантной химиотерапии у больных тройным негативным раком молочной железы

Бабышкина Н.Н.[1, 2], Дронова Т.А.[1, 2], Замбалова Е.А.[1], Завьялова М.В.[1, 2, 3], Слонимская Е.М.[1, 3], Чердынцева Н.В.[1, 2]

[1] *Научно-исследовательский институт (НИИ) онкологии, Томский национальный исследовательский медицинский центр (ТНИМЦ) Российской академии наук*
Россия, 634050, г. Томск, пер. Кооперативный, 5

[2] *Национальный исследовательский Томский государственный университет (НИ ТГУ)*
Россия, 634050, г. Томск, пр. Ленина, 36

[3] *Сибирский государственный медицинский университет (СибГМУ)*
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Актуальность. Выявление предсказательных молекулярных маркеров тройного негативного рака молочной железы позволит оценить эффективность неоадъювантной химиотерапии (НАХТ) и определить оптимальные подходы к прогнозированию течения заболевания.

Цель исследования. Изучить взаимосвязь экспрессии рецептора эпидермального фактора роста EGFR и полиморфных вариантов его гена с эффективностью неоадъювантной химиотерапии у больных тройным негативным раком молочной железы.

Материалы и методы. В исследование включены 70 пациенток с тройным негативным раком молочной железы, получавших 2–4 курса НАХТ по схеме FAC или CAX. Оценка эффективности НАХТ проводилась по шкале RECIST. Уровень экспрессии EGFR в опухоли до и после НАХТ оценивался иммуногистохимическим методом. Анализ полиморфных вариантов гена *EGFR* в локусах rs2227983 и rs1468727 проведен с помощью полимеразной цепной реакции в режиме реального времени.

Результаты. Выявлено, что в процессе НАХТ уровень экспрессии EGFR в опухоли значимо снижается ($p = 0{,}000$). Показано, что достижение объективного клинического и полного патоморфологического ответа опухоли ассоциировано с низким уровнем экспрессии EGFR ($p = 0{,}007$ и $p = 0{,}000$ соответственно). Отсутствие эффективного ответа на НАХТ у больных тройным негативным раком молочной железы связано с носительством мутантных генотипов EGFRCC в локусе rs1468727 ($p = 0{,}042$). Кроме того, среди пациентов, несущих мутантный вариант гена *EGFR*CC, чаще встречаются опухоли с высокой экспрессией *EGFR* по сравнению с больными, имеющими дикий вариант *EGFRTT* ($p = 0{,}047$).

Заключение. Уровень экспрессии EGFR в опухоли и полиморфные варианты его гена в локусе rs1468727 могут рассматриваться в качестве потенциальных молекулярных маркеров с предсказательной значимостью в отношении эффективности НАХТ у больных тройным негативным раком молочной железы.

Ключевые слова: тройной негативный рак молочной железы, неоадъювантная химиотерапия, рецептор эпидермального фактора роста EGFR, полиморфизм генов.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа выполнена при финансовой поддержке гранта РНФ № 19-75-30016 «Новая технология прогнозирования и профилактики отдаленного метастазирования на основе детекции циркулирующих метастаз-инициирующих и нишеобразующих клеток и их специфических мишеней».

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Работа проведена согласно принципам добровольности и конфиденциальности в соответствии с «Основами законодательства РФ об охране здоровья граждан (Указ Президента РФ от 24.12.93 № 2288) на основании разрешения локального комитета по биомедицинской этике НИИ онкологии Томского НИМЦ.

Для цитирования: Бабышкина Н.Н., Дронова Т.А., Замбалова Е.А., Завьялова М.В., Слонимская Е.М., Чердынцева Н.В. Роль рецептора эпидермального фактора роста EGFR в эффективности неоадъювантной химиотерапии у больных тройным негативным раком молочной железы. *Бюллетень сибирской медицины.* 2020; 19 (1): 13–20. https://doi.org: 10.20538/1682-0363-2020-1-13–20.

INTRODUCTION

The triple-negative subtype occupies a special place in the structure of breast cancer morbidity, since it is characterized by an aggressive course of the disease and has an unfavorable prognosis for survival [1–3]. The most significant feature of triple-negative breast cancer (TNBC) is the absence of targets for hormone therapy and targeted therapy with Herceptin, which drastically complicates the treatment of this disease. Today, antitumor systemic therapy is one of the main stages of the TNBC complex treatment. When using neoadjuvant chemotherapy (NACT) cytotoxic drugs facilitate tumor shrinkage, which allows clinicians to perform organ-preserving operations and preserve healthy breast tissue to the maximum degree posible. However, a pathologic complete tumor response is observed only in 12–30% of patients [4, 5]. Thus, the search for additional prognostic markers of sensitivity and resistance to various groups of cytostatics, allowing to individualize therapeutic approaches for TNBC patients, remains an urgent task.

One of the molecular markers that has been actively studied in recent years is the epidermal growth factor receptor (EGFR), a transmembrane glycoprotein involved in the regulation of cell growth and malignant transformation. It is generally recognized that the amplification and / or overexpression of EGFR leads to the development of resistance to endocrine therapy in estrogen-dependent tumors [6, 7]. Our recent studies showed the prognostic significance of tamoxifen and demonstrated that patients resistant to tamoxifen therapy had a high level of EGFR expression in tumors [8]. In estrogen-independent tumors, EGFR overexpression is more a result of the increased number of gene copies due to polysomy than due to activating mutations or EGFR amplification and is usually associated with disease progression and low patient survival rates [9, 10]. It is worth noting that a large number of studies have been devoted to the prognostic value of EGFR expression in TNBC patients [11–14]. However, the contribution of functionally significant polymorphic sites of the EGFR gene in comparison with the expression level of its protein product in the mechanisms of resistance to neoadjuvant chemotherapy currently remains under-researched.

The aim of the study was to examine the correlation between the expression of the epidermal growth factor receptor (EGFR), functionally significant polymorphic variants of its gene and the neoadjuvant chemotherapy (NACT) efficacy in triple-negative breast cancer (TNBC) patients.

MATERIALS AND METHODS

The study included 70 patients aged 28–69 with a verified diagnosis of triple-negative breast cancer. The patients were undergoing treatment in the General Oncology Department of the Cancer Research Institute, Tomsk National Research Medical Center (NRMC) in the period from 2007 to 2013. All patients were treated with neoadjuvant polychemotherapy comprised of 2–4 cycles of FAC (5-fluorouracil 500 mg/m^2 on day 1, Adriamycin 50 mg/m^2 on day 1, cyclophosphamide 500 mg/m^2 on day 1, IV; the interval between courses is 21 days) or CAX regimen (cyclophosphamide 100 mg/m^2 IM for 14 days, Adriamycin 30 mg/m^2 IV on days

1, 8; Xeloda 1000 mg/m^2 2 times/day, per os, for 14 days; the interval between courses is 21 days) followed by surgical treatment (in the scope of radical resection, sector resection with axillary lymph node dissection (ALND) or radical mastectomy). Courses of polychemotherapy (FAC) and radiation therapy were given according to the indications in the adjuvant mode.

The NACT efficacy was assessed according to the RECIST scale. An objective clinical response was measured by the sum of complete and partial regressions of the breast tumor. The presence of disease stabilization and disease progression was considered as a lack of efficacy. The severity of drug pathomorphism in breast tissue and regional lymph nodes was evaluated conforming to the classification proposed by E.F. Lushnikov (1977) [15]. Patients were diagnosed with "complete morphological regression" when there were no tumor elements both in the breast tissue and in the lymph nodes under study. The follow-up period was 12–80 months.

In order to study the polymorphic variants of the EGFR gene, DNA was extracted from peripheral blood samples using the QIAamp DNA Mini Kits (50) (Qiagen). Qualitative and quantitative assessment of DNA was carried out on a NanoDrop-1000 spectrophotometer (NanoDrop, USA). Polymorphic variants of the EGFR gene at the rs2227983 and rs1468727 loci were studied using real-time polymerase chain reaction (PCR) using the TaqMan technology.

The sequences of primers and samples were selected by the OligoAnalysisVector NTI program using a genetic database (www.ncbi.nlm.nih.gov). The 15 μl PCR reaction mixture included 100 ng of genomic DNA; 0.5–1.5 μl of a specific pair of primers and samples with a concentration of 1 PFU / ml; 200 μm of each deoxynucleotide triphosphate; 1.2–2.0 μl of buffer (60 mM Tris-HCl (pH 8.5 at 25 °C), 1.5 mM MgCl2; 25 mM MKCl; 10 mM 2-Mercaptoethanol; 0.1% Triton X-100) and 0.5–1.0 units Taq DNA polymerase ("Medigen", Novosibirsk). The amplification program included initial denaturation at 95 °C for 2 min, followed by 40 cycles at 95 °C (10 s), annealing at a specific temperature for each pair of primers (30 s) on a CFX96 thermal cycler (Bio-Ra, USA).

The EGFR expression level in the tumor before and after NACT was studied on paraffin sections using the immunohistochemical method. Antibodies to EGFR (clone SP9, working dilution 1: 100) from Novus Biologicals were used. The results of immunohistochemical reactions were evaluated semi-quantitatively, depending on the proportion (%) of positively stained cells and their staining intensity in at least 10 areas of each section at 400x magnification. The staining intensity was evaluated on a scale of 0 to 3, when 0 was defined as negative staining, 1+ as weak staining, 2+ as moderate staining, and 3+ as strong staining. Sections with moderate (2+) or strong (3+) cytoplasmic and / or membrane staining in more than 10% of the cells were considered EGFR-positive, sections with negative staining (0) or weak (1+) expression in less than 10% of the cells were considered EGFR-negative.

SPSS 21.0 (IBM SPSS Statistics, Armonk, NY, USA) was used to analyze the obtained data. The distribution of genotypes of the studied genes was checked for compliance with the Hardy-Weinberg equilibrium. A two-way F-test was used to compare the frequencies of alleles and genotypes of the EGFR gene, to assess their correlation with the level of EGFR expression, as well as to analyze the correlation between the level of EGFR expression and the NACT efficacy. If the number of observations in the contingency table was more than 5, then χ^2 with the Yates correction was taken into account. Differences were considered reliable when at a significance level of $p < 0.05$.

RESULTS

To analyze changes in the EGFR expression level in a tumor, we studied the content of cells with negative and positive expression in biopsy samples before neoadjuvant chemotherapy and in postoperative samples after treatment. It was discovered that the EGFR expression indices had significantly changed during the course of NACT. So, the number of cells with positive EGFR expression decreased from 85.7 to 44.8%; the number of EGFR-negative cells, in contrast, increased from 14.3 to 55.2% ($p = 0.000$, Fig. 1). Since it was found that NACT leads to a decreased EGFR expression level, we analyzed how these expression features were connected with the tumor response to therapy. It was revealed that a high frequency of both objective clinical and pathological complete responses of tumor was observed in patients with a low EGFR expression level ($p = 0.007$ and $p = 0.000$, respectively, Fig. 2).

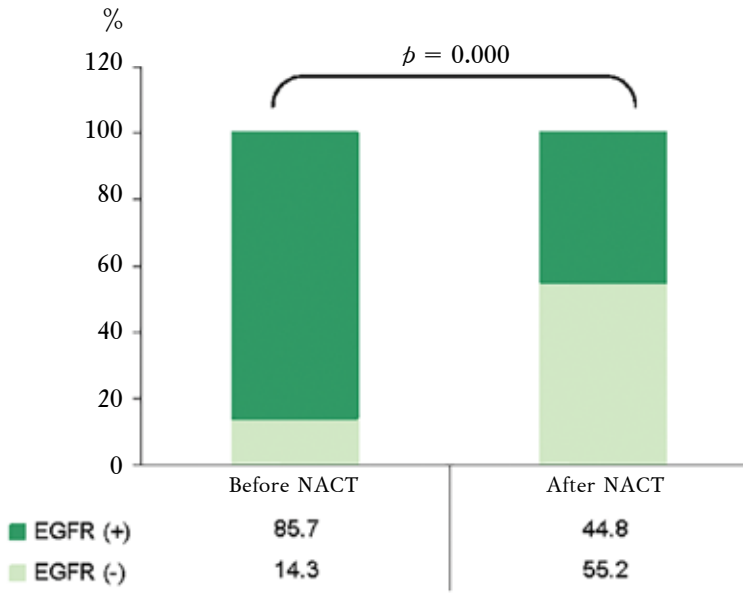

Fig. 1. The EGFR expression level in the tumor tissue before (*a*) and after (*b*) neoadjuvant chemotherapy

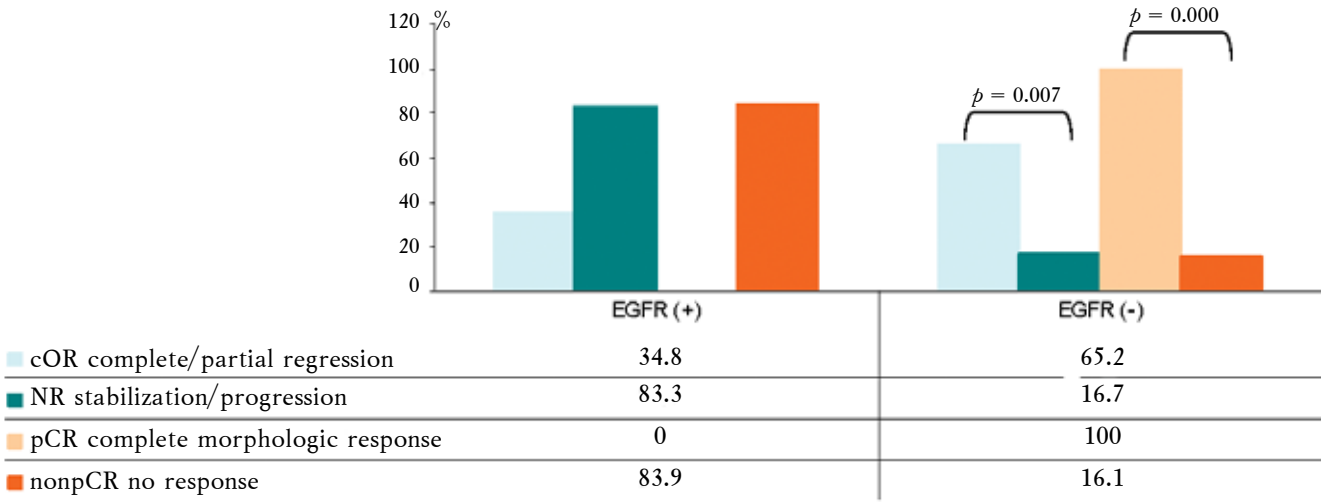

Fig. 2. The correlation between the EGFR expression level in the tumor tissue and the NACT efficacy

Next, in order to assess their possible involvement in triggering sensitivity and resistance mechanisms of the tumor to NACT, polymorphic variants of the EGFR gene were studied at the two loci (rs1468727 and rs2227983) in the peripheral blood samples of TNBC patients. An analysis of objective clinical response revealed that the frequency of occurrence of the mutant EGFRCC genotype at the rs1468727 locus in patients with stabilization or disease progression was more than 2 times higher than that in patients with complete or partial regression, however, without statistical differences ($p = 0.114$, Table 1). The study of complete morphological regressions made it possible to associate this mutant variant with an inefficacious tumor response ($p = 0.042$, Table).

We analyzed the correlation between the EGFR polymorphic variants under study and the expression level of the protein encoded by it. It was discovered that carriers of mutant EGFRCC genotypes of rs1468727 more often had positive expression of EGFR in the tumor before NACT when compared with carriers of the wild-type EGFR gene ($p = 0.047$, Fig. 3). After NACT, positive expression of EGFR in the tumor was found in all patients (100%) having mutations in this polymorphic locus ($p = 0.038$, Fig. 3).

Table

The correlation between the *EGFR* polymorphisms and NACT efficacy

Genotype/ allele	Objective clinical response, *n* (%)				Pathological complete response, *n* (%)			
	Complete/ partial	Stabilization/ progression	OR (95% CI)	*p*	Complete response	No response	OR (95% CI)	*p*
EGFR (rs1468727)								
TT	25 (54.4)	7 (46.7)	1.00		12 (54.5)	20 (51.3)	1.00	
TC	17 (36.9)	5 (33.3)	1.00		10 (45.5)	12 (30.8)	1.00	
CC	4 (8.7)	3 (20.0)	0.38(0.06–2.54)	0.348	0 (0.0)	7 (17.9)	1.22(1.05–1.44)	0.042[1]
T	67 (72.8)	19 (63.3)	1.00		34 (77.3)	52 (66.7)	1.00	
C	25 (27.2)	11 (36.7)	0.64(0.25–1.69)	0.322	10 (22.7)	26 (33.3)	0.59(0.23–1.48)	0.217
EGFR (rs2227983)								
GG	25 (54.4)	7 (46.7)	1.00		12 (54.5)	20 (51.3)	1.00	
GA	19 (41.3)	6 (40.0)	1.00		10 (45.5)	15 (38.5)	1.00	
AA	2 (4.3)	2 (13.3)	0.30(0.03–3.34)	0.251	0 (0.0)	4 (10.2)	1.11(1.00–1.24)	0.287
G	69 (75.0)	20 (66.6)	1.00		34 (77.3)	55 (70.6)	1.00	
A	23 (25.0)	10 (33.4)	0.67(0.25–1.79)	0.372	10 (22.7)	23 (29.4)	0.70(0.27–1.79)	0.420

[1] differences of indices between groups “complete response” and “no response”.

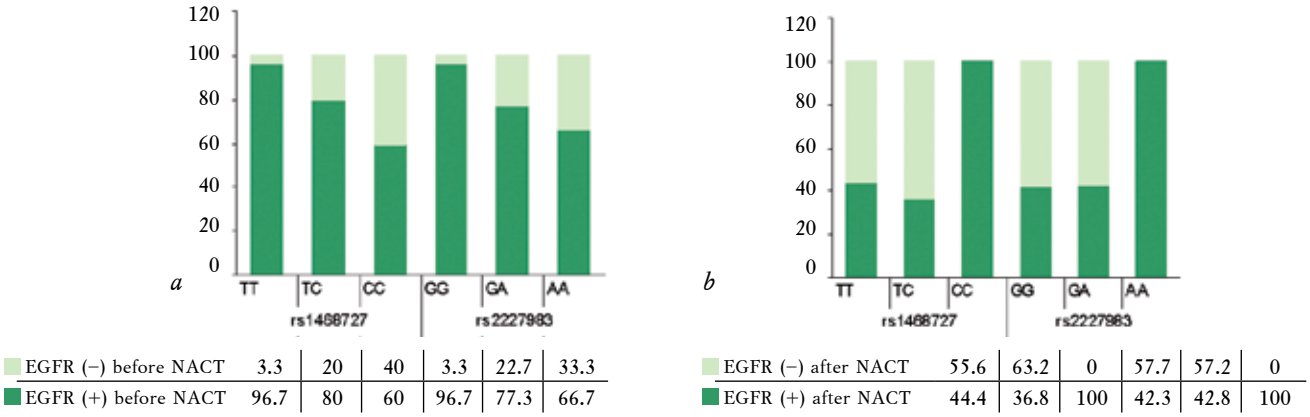

Fig. 3. The correlation between the EGFR expression level in the tumor tissue before (*a*) and after (*b*) neoadjuvant chemotherapy and the EGFR polymorphisms

DISCUSSION

The study showed a significant decrease in the level of EGFR expression in the tumor during NACT, which is associated with an objective clinical and pathological complete response of the tumor. Literary sources confirm the obtained data. It is known that the use of standard combinations of alkylating agents and taxanes for the treatment of locally advanced or metastatic breast cancer leads to a decrease in the initially high level of EGFR expression, which has prognostic significance [16]. In addition, the EGFR expression level is currently being considered as a potential predictive marker of response to NACT in TNBC patients [17].

Our study associates the lack of an effective response to preoperative chemotherapy in TNBC patients with their mutant EGFR genotypes of rs1468727. It is known that the polymorphic variant of rs1468727 affects the intron region of EGFR and does not directly alter the amino acid sequence of the protein. However, mutations within introns may significantly influence transcription and RNA stability. A mutant variant of the EGFRCC (rs1468727) may be connected with an increase in receptor activity, its expression or stability, which leads to the activation of EGFR-mediated signals and significantly increased proliferative potential of the tumor [18]. Our studies confirm this hypothesis since the mutant EGFRCC genotype is

related to no tumor response to NACT. It is important to note that tumors in 60% of patients with this mutation are characterized by positive expression of EGFR. A high level of EGFR expression may contribute to the activation of numerous intracellular messengers, including PI3K / Akt, Ras / MAPK, STAT, which stimulates proliferative processes, increases the invasive potential of the tumor, and eventually contributes to ineffective treatment. It should be noted that the EGFR gene polymorphism under study is scarcely described in the literature. It is only the connection of the rs1468727 mutation and the prognosis of gliomas that has been demonstrated [19].

CONCLUSION

The NACT efficacy in TNBC patients is associated with the genotypic and phenotypic features of EGFR. The mechanisms of ineffectiveness of neoadjuvant chemotherapy can be caused by the EGFR mutation of rs1468727, which leads to the high expression activity of the receptor. This determines the realization of EGFR-mediated signaling cascades providing tumor proliferative potential. The decreased EGFR expression level in tumor tissue after NACT and the polymorphic variants of the EGFR gene (rs1468727) can be considered as potential molecular criteria related to the effectiveness of neoadjuvant chemotherapy in TNBC patients.

REFERENCES

1. De Ruijter T.C., Veeck J., de Hoon J.P., van Engeland M., Tjan-Heijnen V.C. Characteristics of triple-negative breast cancer. *Clin. Oncol.* 2011; 137 (2): 183–192. DOI: 10.1007/s00432-010-0957-x.
2. Wahba H.A., El-Hadaad H.A. Current approaches in treatment of triple-negative breast cancer. *Cancer Biol. Med.* 2015; 12 (2): 106–116. DOI: 10.7497/j.issn.2095-3941.2015.0030.
3. Oualla K., El-Zawahry H.M., Arun B., Reuben J.M., Woodward W.A., Gamal El-Din H., Lim B., Mellas N., Ueno N.T., Fouad T.M. Novel therapeutic strategies in the treatment of triple-negative breast cancer. *Ther. Adv. Med. Oncol.* 2017; 9 (7): 493–511. DOI: 10.1177/1758834017711380.
4. Voduc K.D., Cheang M.C., Tyldesley S., Gelmon K., Nielsen T.O., Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. *Journal of Clinical Oncology.* 2010; 28 (10): 1684–1691. DOI: 10.1200/JCO.2009.24.9284.
5. Cortazar P., Zhang L., Untch M., Mehta K., Costantino J.P., Wolmark N., Bonnefoi H., Cameron D., Gianni L., Valagussa P., Swain S.M., Prowell T., Loibl S., Wickerham D.L., Bogaerts J., Baselga J., Perou C., Blumenthal G., Blohmer J., Mamounas E.P., Bergh J., Semiglazov V., Justice R., Eidtmann H., Paik S., Piccart M., Sridhara R., Fasching P.A., Slaets L., Tang S., Gerber B., Geyer C.E. Jr., Pazdur R., Ditsch N., Rastogi P., Eiermann W., von Minckwitz G. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014; 384 (9938): 164–72. DOI: 10.1016/S0140-6736(13)62422-8.
6. Osborne C.K., Schiff R. Mechanisms of endocrine resistance in breast cancer. *Ann. Rev. Med.* 2011; 62: 233–247. DOI: 10.1146/annurev-med-070909-182917.
7. Chong K., Subramanian A., Sharma A., Mokbel K. Measuring IGF-1, ER-α and EGFR expression can predict tamoxifen-resistance in ER-positive breast cancer. *Anticancer Res.* 2011; 31 (1): 23–32.
8. Dronova T.A., Babyshkina N.N., Zavyalova M.V., Patalyak S.V., Slonimskaya E.M., Cherdyntseva N.V., Kzhyshkowska J.G. Relation of EGFR/PI3K/AKT signaling components with tamoxifen efficacy in patients with estrogen-dependent breast cancer. *Advances in Molecular Oncology.* 2018; 5 (3): 40–50. (In Russ.). DOI: 10.17650/2313-805X-2018-5-3-40-50.
9. Tischkowitz M., Brunet J.S.,Begin L.R., Huntsman D.G., Cheang M.C., Akslen L.A., Nielsen T.O., Foulkes W.D. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. *BMC Cancer.* 2007; 7:134. DOI: 10.1186/1471-2407-7-134.
10. Park H.S., Jang M.H., Kim E.J., Kim H.J., Lee H.J., Kim Y.J., Kim J.H., Kang E., Kim S.W., Kim I.A., Park S.Y. High EGFR gene copy number predicts poor outcome in triple-negative breast cancer. *Mod. Pathol.* 2014; 27 (9): 1212–1222. DOI: 10.1038/modpathol.2013.251.
11. Zhang M., Zhang X., Zhao S., Wang Y., Di W., Zhao G., Yang M., Zhang Q. Prognostic value of survivin and EGFR protein expression in triple-negative breast cancer (TNBC) patients. *Target Oncol.* 2014; 9 (4): 349–357. DOI: 10.1007/s11523-013-0300-y.
12. Yue Y., Astvatsaturyan K., Cui X., Zhang X., Fraass B., Bose S. Stratification of prognosis of triple-negative breast cancer patients using combinatorial biomarkers. *PLoS One.* 2016; 11 (3): e0149661. DOI: 10.1371/journal.pone.0149661.
13. Abdelrahman A.E., Rashed H.E., Abdelgawad M., Abdelhamid M. Prognostic impact of EGFR and cytokeratin 5/6 immunohistochemical expression in triple-negative breast cancer. *Ann. Diagn. Pathol.* 2017; 28: 43–53. DOI: 10.1016/j.anndiagpath.2017.01.009.
14. Foidart P., Yip C., Radermacher J., Blacher S., Lienard M., Montero-Ruiz L., Maquoi E., Montaudon E., Chвteau-Joubert S., Collignon J., Coibion M., Jossa V., Marangoni E., Noʌl A., Sounni N.E., Jerusalem G. Expression of MT4-MMP, EGFR, and RB in triple-negative breast cancer strongly sensitizes tumors to erlotinib and palbociclib combination therapy. *Clin. Cancer Res.*

2019; 25 (6): 1838–1850. DOI: 10.1158/1078-0432.CCR-18-1880.
15. Lushnikov E.F. Luchevoy patomorfoz opukholey cheloveka. Moscow: Meditsina; 1977: 328 (in Russ.).
16. Van Reesema L.L.S., Zheleva V., Winston J.S., Jansen R.J., O'Connor C.F., Isbell A.J., Bian M., Qin R., Bassett P.T., Hinson V.J., Dorsch K.A., Kirby B.W., van Sciver R.E., Tang-Tan A.M., Harden E.A., Chang D.Z., Allen C.A., Perry R.R., Hoefer R.A., Tang A.H. SIAH and EGFR, two RAS pathway biomarkers, are highly prognostic in locally advanced and metastatic breast cancer. *EBioMedicine*. 2016; 11: 183–198. DOI: 10.1016/j.ebiom.2016.08.014.
17. Tang Y., Zhu L., Li Y., Ji J., Li J., Yuan F., Wang D., Chen W., Huang O., Chen X., Wu J., Shen K., Loo W.T., Chow L.W. Overexpression of epithelial growth factor receptor (EGFR) predicts better response to neo-adjuvant chemotherapy in patients with triple-negative breast cancer. *J. Transl. Med.* 2012; 10 (1): S4. DOI: 10.1186/1479-5876-10-S1-S4.
18. Li B., Zhao W., Li J., Yan M., Xie Z., Zhu Y., Chen C., Jin T. Effect of epidermal growth factor receptor gene polymorphisms on prognosis inglioma patients. *Oncotarget*. 2016; 7 (39): 63054–63064. DOI: 10.18632/oncotarget.10666.
19. Wang X., Zhang H., Wang D., Li X. Association of genetic polymorphisms of EGFR with glioma in a Chinese population. *Genet. Test Mol. Biomarkers*. 2015; 19 (1): 59–62. DOI: 10.1089/gtmb.2014.0228.

Authors contribution

Babyshkina N.N. – conception and design, analysis and interpretation of data. Dronova T.A. – analysis and interpretation of data. Zambalova E.A. – analysis and interpretation of data, literature review. Zavyalova M.V. – analysis and interpretation of data. Slonimskaya E.M. – conception and design. Cherdyntseva N.V. – conception and design.

Authors information

Babyshkina Nataliya N., Cand. Sci. (Med.), Senior Researcher, Laboratory of Molecular Oncology and Immunology, Cancer Research Institute, Tomsk National Research Medical Center, Tomsk. ORCID 0000-0002-0562-3878.

Dronova Tatyana A., Post-Graduate Student, Laboratory of Molecular Oncology and Immunology, Cancer Research Institute, Tomsk National Research Medical Center, Tomsk. ORCID 0000-0003-3009-2404.

Zambalova Elena A., Post-Graduate Student, National Research Tomsk State University, Junior Researcher, Laboratory of Tumor Biochemistry, Cancer Research Institute, Tomsk National Research Medical Center, Tomsk. ORCID 0000-0003-3698-8455.

Zavyalova Marina V., Dr. Sci. (Med.), Professor, Head of the Pathological Anatomy Division, Siberian State Medical University, Tomsk. ORCID 0000-0001-9429-9813.

Cherdyntseva Nadezhda V., Dr. Sci. (Biology), Professor, Corresponding Member of the Russian Academy of Sciences, Head of the Division of Molecular Oncology and Immunology of Cancer Research Institute, Tomsk National Research Medical Center, Tomsk. ORCID 0000-0003-1526-9013.

Slonimskaya Elena M., Dr. Sci. (Med.), Professor, Head of the Division of General Oncology, Cancer Research Institute, Tomsk National Research Medical Center, Tomsk. ORCID 0000-0003-4382-5697.

(✉) **Babyshkina Nataliya N.**, e-mail: nbabyshkina@mail.ru.

Received 19.03.2019
Accepted 25.12.2019