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METFORMIN AS ADJUVANT OPTION FOR SYSTEMIC TREATMENT OF BREAST CANCER

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Abstract. Metformin as an adjuvant option for systemic treatment of breast cancer. Avierin D.I., Zavizion V.F. *The modification of the used and development of new treatment regimens significantly improved the overall, recurrence-free survival and quality of life of patients with malignant oncological diseases. Recently, drugs used in non-oncological pathology have been introduced into cancer treatment regimens. This phenomenon is associated with a better understanding of the biology of tumor cells and the mutations that can change this biology. Metformin is actively researched in terms of the treatment of various oncological diseases. For the most part, the modification of the neoadjuvant treatment regimen for early or locally advanced stages of breast cancer results in a less traumatic variant of surgical procedure, thereby increasing recurrence-free survival. The aim is to systematize the data on the possibilities of the antitumor metformin usage for neoadjuvant treatment of breast cancer and to study the results of clinical and morphological effectiveness of the treatment by reviewing the literature. A search of PubMed from February 2023 showed 258 results on the antitumor effects of metformin, of which only 159 were published in the last 5 years. On this subject only four clinical studies were carried out, and only one of them pertained to the implementation of metformin in the systemic treatment of breast cancer. For this review, 55 sources of general and specialized information on anticancer effects of metformin were analyzed. It should be noted that approximately 60% of the study results were published more than 5 years ago and primarily focused on the biological, not clinical aspects of metformin usage. Only one study regarding the implementation of metformin for systemic treatment of breast cancer was carried out by Ukrainian scientists. Currently, there are 2 main hypotheses regarding the antitumor effect of metformin. First one is driven by its impact on the metabolic function of cells and energy deficit. Second – the method of regulating the proliferation of tumor cells involves the PIK3 branch of the regulatory cascade of biological reactions in cancer cells. In addition, metformin reduces the development of resistance in breast cancer cells, thus allowing active chemotherapy agents to act in synergism. However, further studies on the effect of metformin used alone or in combination with standard chemotherapy regimens require a more adequate definition of proto-oncogenic mutations and somatic mutation load. However, it should be considered that more aggressive therapy of oncological diseases can be a nosocomial selector of more aggressive clones of the pool of tumor cells. The main questions are whether metformin can be a targeted drug for the treatment of tumor, whether it is appropriate to use it at the time when the manifestation of evolution disturbances of tumor cell is minimal and homogeneity is maximal.*

Реферат. Метформін як ад'ювант системного лікування раку молочної залози. Аверін Д.І., Завізіон В.Ф. *Модифікація старих та створення нових схем лікування значно покращили загальну, безрецидивну виживаність та якість життя хворих на злоякісні онкологічні захворювання. Останнім часом упроваджено ліки, що використовуються при неонкологічній патології, до схем лікування онкологічних захворювань. Цей феномен пов'язаний з кращим розумінням біології пухлинних клітин та мутацій, які можуть змінювати цю біологію. Метформін активно досліджується в аспекті лікування різних онкологічних захворювань. Здебільшого модифікація неоад'ювантного режиму лікування локальних або локально поширених стадій раку молочної залози вже призводить до менш травматичного варіанту хірургічного етапу та тим самим збільшує безрецидивну виживаність. Мета – систематизувати дані щодо можливостей протипухлинного використання метформіну для неоад'ювантного лікування раку молочної залози та вивчення результатів дослідження клінічної та морфологічної ефективності лікування шляхом огляду літератури. За пошуком PubMed NCBI від лютого 2023 року відображено 258 результатів щодо протипухлинної дії метформіну, з них тільки 159 були опубліковані за останні 5 років. Клінічних досліджень за темою пошуку було проведено тільки 4 та тільки одне щодо впровадження його до системного лікування раку молочної залози. Для написання огляду було використано аналіз 47 джерел загальної та спеціалізованої інформації. Близько 60% результатів усіх досліджень були представлені більше ніж 5 років тому та відображають перш за все біологічні, а не клінічні аспекти використання метформіну. Лише одне дослідження було проведено вітчизняними вченими щодо імплементації метформіну до системного лікування раку молочної залози. Наразі існує 2 принципові гіпотези щодо протипухлинного ефекту метформіну. Перша зумовлена впливом на метаболічну функцію клітин та енергетичний дефіцит. Друга зумовлена впливом на фосфатидилінозитол-3-кінази (PIK3) шлях регуляції проліферації пухлинних клітин. Крім того, метформін зменшує розвиток резистентності в клітинах раку молочної залози (РМЗ), тим самим дозволяючи активним хіміотерапевтичним засобам діяти синергічно з ним. Проте подальші дослідження впливу метформіну, який використовується окремо або в комбінації зі стандартними схемами хіміотерапії, вимагають більш детального визначення протоонкогенних мутацій і соматичного мутаційного навантаження. Проте слід ураховувати, що більш агресивна терапія онкологічних захворювань може бути нозокоміальним селектором більш агресивних клонів пулу пухлинних клітин. Головними залишаються питання: чи зможе метформін бути таргетним препаратом для лікування пухлинних захворювань та чи доцільне його використання в той момент, коли вираженість еволюційних порушень пухлинних клітин мінімальна, а гомогенність максимальна.*

A fair number of fundamental and clinical research on tumor biology and tumor resistance to treatment has been accumulated over the past ten years. The result is a deeper understanding of the biology of tumor growth and, therefore, the methods of treatment that can be implemented in the therapy of oncological diseases. Thus, cellular senescence, phenotypic plasticity, epigenetic reprogramming, and the influence of polymorphic microbiota were added to the already existing theses regarding tumor biology. These theses make it clear that the border between a normal cell and a tumor cell is becoming less and less visible. In the context of the latest data, the main question is not which processes are key for carcinogenesis, but how the tumor manages to chimerize the biological processes of cellular life. Eventually, there are fewer gray questions in the understanding of the nature of the tumor, but new ones appear instead of the old ones, which can cause new questions that, in the final understanding, can change the paradigm of treatment of malignant tumors [1, 2, 3, 4].

The key to this is the non-mutational epigenetic reprogramming of cells, both normal and oncological. Thanks to this, the cell is able to selectively transcribe a strictly defined set of genes. In a tumor, epigenetic regulation, combined with gene mutations and gene instability, produces a unique molecular-genetic landscape that underlies the formation of the cell, its life and, as a result, its treatment. It should be noted that epigenetic regulation affects:

• signaling cascades that can provoke cell proliferation and cause resistance to chemopreparations (the PI3K/AKT/mTOR pathway);

• glucose metabolism and strengthen the Warburg effect;

• hypomethylation of genes implementing epithelial-mesenchymal transition reactions;

• expression of genes whose proteins can be used for antigen presentation and perform a target role for T-cytotoxic lymphocytes [1].

Cancer and diabetes are two of the most common chronic diseases worldwide, which are strongly linked. Diabetes mellitus is a significant factor in the unfavorable prognosis for many groups of patients with an oncological, infectious, cardiology profile, etc. Many epidemiological studies show a significant increase in the risk of developing cancer against the background of diabetes [2, 3].

There is substantial evidence that the risk of developing and dying from breast cancer is higher in diabetics compared to nondiabetics, excluding all other diseases. There are enough publications and meta-analyses linking increased survival and the use of antidiabetic drugs in patients with breast cancer and diabetes [4, 5]. Thus, the increased risks of the development of BC among the population of patients with diabetes mellitus (DM) were found in retrospective and prospective studies (SRR 1.36 (95% CI, 1.13–1.63)) versus 1.27 (95% confidence interval (CI), 1.16–1.39) [48].

According to the Centers for Disease Control and Prevention (CDC) and National Comprehensive Cancer Network (NCCN), breast cancer is one of the most common types of cancer in women and represents a significant public health problem. The American Cancer Society estimates that one in eight women will be diagnosed with breast cancer at some point in their lives, and the incidence increases with age [6, 50]. Examining the standardized mortality ratios (SMRs) for each age group, it was found that the younger group of patients with BC had a higher SMR than the older group (SMR 9.68, 95% CI: 8.99to 10.42) versus SMR 3.11, 95% CI: 2.54 to 3.76) [49]. NCCN also reports that 15.2% of people diagnosed with breast cancer die within the first year after diagnosis [6]. The etiology associated with breast cancer is complex and involves interactions between environmental, lifestyle, and genetic factors that together determine tumor risk. As a rule, oncological diseases occur when cells lose the ability to stop the proliferation process in combination with resistance or reduction of the process of cell death by apoptosis.

Neoadjuvant polychemotherapy (NAPCT) in early breast cancer may make breast-conserving surgery more feasible and more likely to eradicate micrometastatic disease than the same chemotherapy given after surgery, adjuvant polychemotherapy (APCT). In a general sense, the issue of using NAPCT can fundamentally change the tactics of further treatment of the patient, make the prognosis more favorable. According to some data, only 15 to 45% of cases, including all immunohistochemical (IHC) types of breast cancer, can achieve a complete pathological response to NAPCT [7, 8].

A significant increase of a number of patients with a complete morphological response (pCR) after the neoadjuvant (NA) therapy can significantly increase the recurrence-free survival (5-year progression-free survival rate, 80% vs. 53%, (p=0.030) and 5-year overall survive (OS) rate, 86% vs. 54%, (p =0.042) than those who did not achieve pCR [53]. That can be reason of disability reduce after surgical treatment, lower levels of cardiotoxicity and neurotoxicity, which can reduce the burden on the financial health care system of the country, government programs or insurance systems and financial toxicity for the patient. This is the most successful justification for changes in the preoperative tactics of treating patients with breast cancer [9, 52]. Thus, among the group of

patients who received NA treatment, the following results were achieved: no stage change =29.1%, stage reduction =7.9%, total pCR=19.2%. The results are associated with improved OS: with triple-negative BC [HR=0.58, 95% confidence interval (95% CI =0.37-0.89), nodal-only pCR was associated with by improvement of OS as with triple negative (HR=0.55, 95% CI=0.39-0.76), with luminal-B, her-2/neu negative (risk ratio =0.54, 95% CI=0.33-0.89). For patients achieving overall (breast and axillar nodes) pCR, unadjusted 5-year OS was 0.94 (95% CI=0.93-0.95), with no difference between patients who were cN0 (hazard ratio =0.95, 95% CI=0.93-0.96) or cN1 (hazard ratio =0.94, 95% CI=0.92-0.96) at diagnosis [51].

One of the clear examples of the need to achieve pCR was a group of patients who started receiving targeted therapy (TT) with trastuzumab and, according to current protocols, should continue TT for 12 months. However, the European Society for Medical Oncology (ESMO) at the Annual Meeting 2021 provided initial convincing data on trastuzumab de-escalation in patients with breast cancer. It should be noted that such tactics can only be correlated with a complete tumor response. A meta-analysis of 3 clinical trials showed non-inferior efficacy of 6 months versus 12 months of adjuvant trastuzumab therapy. But the absolute difference in 5-year recurrence-free survival is 0.7% and requires the search for biomarkers to choose 6 or 12 months of therapy. The data of this meta-analysis should already be discussed with patients, considering the possible balance of benefits and harms [10].

One of these markers can be the achievement of pCR after NA therapy, which was once again demonstrated in another meta-analysis – adding Lapatinib to Trastuzumab in NA not only improves results, but these results also correlate with achieving pCR. Thus, the search for new options for systemic treatment and modifications of existing ones can ultimately change the attitude towards adjuvant therapy for breast cancer and, as a result, reduce the duration of treatment, separate consequences of therapy (cardio and neurotoxicity), and increase the overall life expectancy of cancer patients [11, 12, 13].

Recently, metformin and other hypoglycemic drugs have been studied as modifiers or independent anticancer drugs. This path has already been taken by coffeine for the treatment of soft tissue sarcomas [14]. Studying metformin effects has demonstrated increasing of pCR in the group of patients with the addition of metformin 14.8% versus 6.3% (p-value 0.39) [8]. Considering the analyzed information, three separate clinical questions should be identified separately.

1. Molecular issues. Chronic energy excess and decrease of physical activity led to systemic changes in carbohydrate and fatty acid metabolism characterized by systemic hyperglycemia, hyperinsulinemia with insulin resistance followed by hypoinsulinemia, increased inflammatory cytokines and adipokines, altered steroid and growth hormone levels, and decreased immune surveillance and tissue oxygenation. These changes are common but variable in patients with obesity and type 2 diabetes and can be modified by medications, exercise, weight management, socioeconomic factors, access to health care, genetic risk, and other factors. Patients with these disorders are at increased risk for cardiovascular events, cancer, and other diseases associated with significant morbidity and mortality. In the US, there are ~13.8 million type 2 diabetics, 5 million undiagnosed diabetics, and 41 million individuals with prediabetes/metabolic syndrome [15, 17].

Energy-sensing systems are an integral part of maintaining homeostasis in normal and transformed cells. Energy deficiency is a common phenomenon in cancer cells due to insufficient blood supply to meet the needs of increased cell replication. In energetically stressed cells, AMP-activated protein kinase (AMPK) is allosterically modified by binding to adenosine monophosphoric acid (AMP) and adenosine diphosphoric acid (ADP), making them AMPK target kinases. AMPK activation induces signaling, upregulates energy production, and inhibits energy programming for cell growth and motility. In cancer cells, this shift often does not occur even under stress. As a result, cancer cells tend to prioritize replication and motility to promote cancer growth and metastasis. Agents that activate AMPK, particularly metformin, re-enter AMPK into a protective/normal functioning mode to delay proliferation and motility (migration ability) of cancer cells. [18] It has two proposed antitumor mechanisms: direct (insulin-independent) and indirect (insulin-dependent) action. Metformin is commonly used as a method of combating insulin resistance by reducing the amount of available glucose in the blood in the treatment of type 2 diabetes. Activation of AMPK also affects modulation of adenosine A1 receptor, reduction of insulin and insulin-like growth factor, inhibition of endogenous reactive oxygen species (ROS), which may be associated with damage to the deoxyribonucleic acid (DNA) molecule and is another important antitumor mechanism that should be noted for metformin [16]. Jalving and colleagues rely on the judgment regarding the risk of developing malignant tumors due to insulin resistance through the activation of signaling pathways of insulin-like growth factor in

tumor cells and the strengthening of the role of estrogen receptors [19].

Targeted metabolic mechanisms for cancer treatment have been proposed as a simpler approach than targeting mutated gene substrates to kill all cancer cells at once. Since the degree of metabolic reprogramming that occurs in a cancer cell goes far beyond the regulation of sugar-dependent pathways (Warburg effect), it covers almost all metabolic aspects and takes into account the extremely high biological flexibility of cancer cells, targeting glycolysis or specific metabolic pathways in cancer can be as challenging as targeting somatic mutations [20]. Yamaguchi et al provide evidence on the existence of drugs that can act on a wide spectrum of the cascade of glycolytic metabolism of malignant cells at various stages of the cycle and development, and confirm this in an experiment on cell cultures. However, it is impossible to build a treatment strategy for the patient until the patient's genetic metabolism is analyzed, the range of metabolic pathways is determined, and the use of the drug will not be associated with a randomized "switch" of glycolysis, and on the other hand, the question of the safety of using these inhibitors, since, for example, brain cells have a high-level glycolysis [21].

Cells can escape death from metabolic inhibitors by turning off the glycolytic pathway and switching to aerobic respiration. If cancer cells depend on glycolysis they can easily carry out these metabolic changes to hide among non-proliferative oxidative phosphorylation-dependent normal cells until the treatment ends, then there is a possibility that the metabolic features of cancer cells will return after the treatment with glycolysis inhibitors is stopped [22].

Malignant cells support proliferation, and thus tumor progression in general, by adapting to metabolic changes and finding new proliferation-stimulating factors. Tumor cells are able to change metabolism due to increased absorption of glucose and fermentation of the latter to lactate, regardless of the conditions of oxygen supply. Glucose metabolism in tumor cells is regulated by many factors from protooncogenes mutations to directly carcinogenic factors. Reprogramming of tumor cells is a complex process involving the interaction of different signaling pathways, such as target of rapamycin (mTOR) in mammalians, Akt/phosphatidylinositol 3-kinase (PI3K), PTEN, AMPK. Metformin activates the phosphorylation (AMPK-P) pathway by inhibiting complex 1 of the mitochondrial respiratory chain. Breast adenocarcinoma cells typically express high levels of Akt/phosphatidylinositol-3-kinase (PIK3), a target of signaling pathway of rapamycin (mTOR) in mammalians, which reduces their ability to undergo apoptosis [23]. In studies on cell cultures and with xenotransplants, the dosage of metformin up to 150 mg/kg/day was analyzed in single-mode and in combination with cytostatic drugs and radiation therapy [23] Metformin also induced folate and homocysteine accumulation in both primary tumors stem cells and next-generation cells of the CAMA-1 population, indicating abnormalities in nucleotide synthesis associated with defects in the tetrahydrofolate pathway [54].

Considering the activation of AMPK and the effect on hormone receptors, metformin provides a unique and, as a rule, less toxic effect on the inhibition of cell replication. The ability of metformin to induce cell death in breast cancer germ cells is of significant clinical significance given their role in therapeutic resistance, stabilization, and disease progression. Therefore, there is now more research on potentially effective modification, prevention, and antitumor therapy for many types of cancer [24, 25, 26, 27].

Regarding the study of metformin in the treatment of breast cancer, it reduces the recurrence of cancer by preferentially killing differentiated rather than undifferentiated cancer cells. However, in combination with chemotherapy, metformin is particularly active against undifferentiated cells and more aggressive types of breast cancer (luminal B/triple-negative). Metformin treatment activates AMPKα and inhibits COX-2 expression in breast cancer cells [28].

In studies of cells (in vitro) resistant to trastuzumab, as well as in xenograft models, the combination of trastuzumab and metformin significantly reduced CD44 +, CD24−/low subpopulations (cancer stem cells) and reduced tumor volume. In combination with doxorubicin (A), paclitaxel (T) or carboplatin (P), metformin can also kill germ cells and reduce the effective dose required for highly toxic chemotherapy agents, minimizing the risk of chemotherapy drugs overdose and their cumulative effect. On the other side the dosing of metformin as an anticancer therapy has not been optimized, metformin-based cancer clinical trials are based on its antidiabetic use (850 mg orally once or twice daily). The ability of metformin to inhibit cancer cell proliferation and promote apoptosis requires supraphysiological concentrations of the drug (>5 mM), which are much higher than those used in patients with type 2 diabetes treated with standard metformin [29, 30, 31].

In addition, metformin also reduces the development of resistance in breast cancer cells, thereby allowing active chemotherapy agents to act synergistically with metformin. It also blocks two cellular pathways of nicotinamide adenine dinucleotide (NAD+) regeneration, resulting in complete loss of

NAD+ function in tumor cells. As a result, NAD+ depletion, in turn, leads to cell death [32, 33, 34].

2. Resistance to metformin in the prevention and treatment of breast cancer. Circulating glucose may be an important factor in the response to metformin treatment in cancer patients. Menendez and colleagues reported that the effectiveness of metformin increased in breast cancer cells that had been deprived of glucose [35].

Glucose concentration affects cell signaling and metformin-related changes. As shown by studies performed using 4 representative cell lines T-47D (ER+, PR+, HER2-), SK-BR-3 (ER-, PR-, HER2+), MDA-MB-468 (triple negative) and MDA- MB-231 (triple negative) breast cancer, at a high concentration of glucose, in comparison with cells cultured in its physiological concentrations, cell proliferation, clonogenicity is stimulated, the cell cycle and cell motility are accelerated (migratory properties and the probability of epithelial-mesenchymal transition increase), and apoptosis is suppressed at the same time. In each of the studies, metformin-related changes were generally enhanced at physiological glucose concentrations (up to 6.1 mmol/L) compared to supraphysiological glucose levels. These data substantiate the effect of glucose with or without metformin on changes in the expression and activation of critical signaling molecules. The correlation between the amount of glucose in the culture assays and the expression of Akt, mTOR, STAT3 and ERK was not observed. Elevated glucose levels were associated with increased levels of phosphorylated variants p-mTOR and p-MAPK. As a result of the addition of metformin to the cell cultures, the level of p-Akt, p-mTOR, p-STAT3 decreased significantly, but the levels of mTOR, Akt, Stat3, p-erbB-2 and erbB2, p-EGFR and EGFR, and IGF-1p did not change. These effects were generally observed in cell culture studies under moderate glucose levels of 5 mmol/L to 10 mmol/L, but they were less pronounced in cells cultured at 17 mmol/L. β-actin expression has not correlated with glucose levels or under metformin modification impact. These data indicate that the concentration of glucose in cell cultures can influence both the basal activation of multiple signaling molecules and the efficacy of the addition of metformin to a systemic treatment regimen.

Glucose allows metformin to inhibit procarcinogenic signal transduction more effectively in malignant cells. Metformin protects normal cells at the physiological glucose level, causing inhibition of the life cycle in BC cells. A clear example is the change in the concentration of some RNA molecules (FASN, LSS and GRB2 and INSIG1), which expression depends on the concentration of glucose. A change or, conversely, no change in the concentration of FASN, LSS can correlate with the ability of more resistance and survival of breast cancer cells evolved. Further studies also confirmed that failure to maintain glucose homeostasis leads to a more aggressive triple negative phenotype of BC [36].

These studies showed that metformin protects normal cells in the presence of physiological amounts of glucose, while it induces cell cycle arrest in breast cancer cells. Conversely, glucose disposal induced breast cancer cell death, regardless of the following subtypes: ER +, HER2 + and triple negative. Moreover, under hyperglycemic conditions an excess supply of glucose rescue triple-negative MDA-MD-231 from damaging factors induced by cell death. It is hypothesized that this is due to the production of sufficient energy for proliferation by aerobic glycolysis using excess glucose. Further studies also confirmed that failure to maintain glucose homeostasis leads to a more aggressive triple-negative breast cancer phenotype [37].

Resistance to treatment is inherent in breast cancer, and metformin appears to be no exception. Menendez's group used chronic metformin exposure to establish metformin-resistant cells. In general, there are 3 main questions regarding the use of metformin for the treatment of malignant tumors:

1. This is a rather different concentration of metformin in plasma and in tissues, including tumor and different microenvironment of the tumor and transplants – which can give a significant error in the interpretation of data from xenograft models to a real clinical trial.

2. Rather imprecise and diverse interpretation of studies and pharmacodynamics. Solving this issue will help to understand the exact mechanism of interaction and optimize the rational use of metformin, its dosage, and regimen.

3. A major challenge in dosing and/or administering metformin to optimize plasma drug levels is how to ensure that high concentrations of metformin induce tumor regression with minimal toxicity to normal tissue.

4. Identification of predictive biomarkers of metformin response and accurate patient selection are important to ensure that the true response rate is measured without bias by including patients who do not respond to metformin simply because they are not suitable candidates to benefit from it. The vast majority of current metformin-based clinical trials have not selected patients on the basis of a particular biomarker, which may have improved the poor response rate commonly observed [38,39].

Acquired resistance to metformin causes reprogramming of the genetic material/transcriptome in

breast cancer cells. This is closely associated with a high metastatic potential, which complicates treatment due to excessive adaptability to a toxic (chemo-induced) environment. The efficacy of metformin was also reduced in breast cancer overexpressing BRCA-2, a gene associated with the suppressive function of AMPK. The BRCA2 gene is overexpressed in 10% to 20% of breast cancer patients, making it a potential precision therapy for metformin-resistant breast cancer cells. Many promising studies propose a tailored genetic approach targeting specific genetic mutations, such as BRCA-1/2, with combination therapy to reduce acquired metformin resistance, for example, using platinum drugs or olaparib [40].

Usually, initial planning of treatment tactics, including NA chemotherapy, is based on primary biological data and tumor staging. It should be considered that this method can select more aggressive clones of cells, with a general decrease in the tumor burden. In such cases, disease recurrences are treated with a significantly lower tumor response rate. On the other hand, conversion of receptor status after NA treatment and/or differentiation of expression of receptor status or mutational burden is a sign of biological heterogeneity within the same tumor, which is also reflected in PIK_3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) mutation status. In a systematic review and meta-analysis, the overall frequency of discordant PIK_3CA status in primary and metastatic tumors was 9.8% (95% CI 7.0–13.0). This phenomenon in the primary and metastatic tumor has both a direct and an inverse nature. The presence of a PIK_3CA mutation in the metastasis and its absence in the primary tumor is detected with a frequency of 8.9% (95% CI 6.1–12.1) and vice versa with a frequency of 14% (95% CI 11.8–18.2) [55]. Understanding this feature of the disease is important when making therapeutic decisions and further planning studies of the primary and secondary focus. Such a conversion may correlate with a decrease in the response to tumor treatment and the acquisition of resistance to treatment, including in combination with metformin.

Thus, the heterogeneous nature of breast cancer complicates the treatment of the disease. However, in vitro studies strongly support a role for metformin, one of the most commonly used antidiabetic drugs, as a general therapy for most, if not all, subtypes of breast cancer. In addition, the possibility of using metformin as a dual treatment for cancer and diabetes is an important consideration as the comorbidity of cancer and diabetes increases over time worldwide. As highlighted in these in vitro studies, the mechanism of action of metformin is still unclear and affects more than one cellular signaling pathway [41].

3. Clinical option of metformin using in syspemic treatment. Xi and colleagues examined specific breast cancer subtypes and found that the nondiabetic metformin group in patients with luminal-A, luminal-B (HER-2/neu hegative) and luminal-B (HER-2/neu positive) had a better prognosis compared to the non-diabetic group that did not receive metformin. However, in the diabetic groups, only in luminal-A and luminal-B (HER-2/neu positive) type cancer, metformin-treated patients had a better prognosis than metformin-naive group. It should also be noted that the results of the studies demonstrate that body mass index was not an independent prognostic factor. This is a retrospective study with limited factor selection; in addition, there were differences in the timing of medication and the amount of medication used by patients. Glycemic control and degree of disease progression were also unclear; therefore, further prospective studies should be conducted among patients considering dose, regimen, and body mass index.

In independent studies, metformin demonstrated reduced cell proliferation in insulin-resistant patients with the luminal-B subtype of breast cancer, although overall, metformin did not significantly alter cell proliferation in this patient cohort with a mean proportional increase of 4.0% (95% CI, -5.6% to 14.4%) after 4 weeks. Diabetes patients with the HER-2/neu+ subtype had better tumor response rate with metformin therapy by Cox regression analysis (p=0.026, HR=1.42, CI 95% 1.04-1.94) and had better survival rate (p=0.023, HR=0.47, 95% CI 0.24-0.90) [42,43]. In contrast, considering clinical cases of breast cancer patients from 2005 to 2011, Besic and colleagues indicated that long-term use of metformin in diabetes group was not associated with the distribution of breast cancer subtypes (p=0,01) [44]. Min and colleagues studied patients with type 2 diabetes and breast cancer who were treated with metformin monotherapy or monotherapy with other hypoglycemic drugs. Patients in the metformin group had a lower probability of metastases in the lymph nodes than when using other antidiabetic drugs ($p<0.05$). This suggests that metformin can overcome tumor resistance to standard treatments [45]. In contrast, Besic and colleagues found that there was no change in PR expression between the metformin and non-metformin groups. During this study 253 patients were examined (both premenopausal and postmenopausal). It was concluded that the different distribution of breast cancer molecular subtypes in these three groups of patients was due to other breast cancer risk factors, such as patient age or obesity (p=0.01) [44]. Blood glucose monitoring may provide a sufficient basis for

further prediction of adverse effects of metformin in combination with polychemotherapy or targeted therapy and provide some insight into the response of patients to metformin and that pharmacological glucose deprivation combined with metformin treatment may benefit hyperglycemic patients [46, 47].

CONCLUSIONS

1. Medical science has advanced rapidly in the field of cancer treatment, and research groups are constantly searching for and developing new and more effective drugs/methods to treat cancer. However, in a world where cancer is one of the most lethal diseases, it will depend on the results of ongoing clinical trials to determine and recommend whether metformin is feasible and beneficial as a modifier or an independent anticancer drug.
2. Further study of the receptor status for biological profiling of subtypes of breast cancer is required for a more complete study of the interaction of metformin with tumor cells, anticancer drugs, and study of the safety profile. The extrapolation of the metformin studies to the use of hormonal therapy can become an additional evidence base for expanding the use of metformin in the treatment of other oncological diseases.
3. Considering the review of the issues in the article a list of the most of current topical tasks of further research of metformin is formed. On the base of the department of oncology and medical radiology of the Dnipro State Medical University, the clinical aspects of the use of metformin in the NA treatment of breast cancer are being studied from the year 2020 and include consideration of the following issues:

a) safety and toxicity profile;

b) prediction, correction, and treatment of side effects and complications;

c) research on the dependence of the effect on the dose of metformin and the clinical effect, calculation of the dose;

d) analysis and prediction of the clinical effect of breast cancer systemic treatment with the metformin addition;

e) search for clinical and laboratory markers predicting tumor response with the addition of metformin.

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