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INFLUENCE OF CYP2D6 AND ITS POLYMORPHIC FORMS ON THE METABOLISM OF TAMOXIFEN IN THERAPY OF LUMINAL FORMS OF BREAST CANCER

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Annotation. *Tamoxifen belongs to the group of selective estrogen receptor modulators (SERM) and is metabolized by the detoxification system of xenobiotics, and the phenomenon of metabolic activation can be observed at the first stage. CYP2D6 also directly participates in this process, the analysis of polymorphic forms of which can influence the prediction of the effectiveness and toxicity of tamoxifen in the treatment of luminal forms of breast cancer, which is of great importance considering the duration of therapy with this drug. The aim - to analyze scientific literature data on the effect of CYP2D6 and its polymorphs on the metabolism of tamoxifen in the treatment of luminal forms of breast cancer. A retrospective analysis of the literature of scientific databases Scopus, Web of Science, PubMed., MedLines for 2013-2023 was carried out. It is established that CYP2D6 can be considered a predictor of treatment effectiveness only in patients with breast cancer (ER+) who are postmenopausal and receive 20 mg of tamoxifen per day for 5 years and do not have hepatotoxic conditions and CYP2D6 inhibition phenomena, which determines the expediency of genotyping CYP2D6 polymorphic variants in such a group. Long-term therapy with tamoxifen can be complicated by the development of secondary endometrial cancer. Undesirable effects of tamoxifen may also depend on the activity of CYP2D6. Thus, in slow metabolizers, for example, carriers of CYP2D6*3/*4 and CYP2D6*6/*6, a statistically significant increase in the frequency of cases of endometrial hyperplasia was observed. In addition, polymorphisms of other enzymes of the biotransformation system of xenobiotics that participate in both the activation and deactivation of tamoxifen and its metabolites, both the first (CYP3A4, CYP3A5, CYP2B6, CYP2C9, CYP2C19 and CYP2D6) and the second phase (SULT and UGT), remain a promising direction for study. The study of the consequences of the phenomena of iatrogenic cholestasis and drug interactions at the level of CYP2D6, which may affect the metabolism of tamoxifen, also requires a detailed study, taking into account the intensive pharmacotherapy of BC.*
Keywords: *tamoxifen; metabolic activation, CYP2D6, debrisoquine hydroxylase, breast cancer; pharmacogenetics.*

Introduction

The most common oncological disease among women is breast cancer (BC). The rate of development of the incidence of breast cancer is more than 1 million new cases per year. Breast cancer occupies the second place in terms of frequency in the structure of oncological morbidity, including the male population. According to WHO, breast cancer kills more than 500,000 people every year. A high percentage (60-70%) of breast cancer cases is characterized by the expression of estrogen receptors. It is known that estrogens and their metabolites can have a genotoxic and mutagenic effect and also increase the proliferation of breast cancer cells, and therefore the main direction of endocrinotherapy is blocking the hyperestrogen state. Tamoxifen belongs to the group of selective estrogen receptor modulators (SERMs), it binds to ER and thus blocks ER-dependent gene expression there, inhibiting the development and spread of breast cancer. Tamoxifen is metabolized by the detoxification system of xenobiotics, and the phenomenon of metabolic activation can be observed at the first stage [16, 17, 21, 22, 24, 25, 27, 29].

CYP2D6 also directly participates in this process, the analysis of polymorphic forms of which can affect the prognosis of the effectiveness and toxicity of tamoxifen, which is of great importance considering the term of therapy with this drug [2, 3, 6, 8, 10, 12, 37, 39].

The aim - to analyze the data of the scientific literature on the study of the influence of CYP2D6 and its polymorphic forms on the metabolism of tamoxifen in the treatment of luminal forms of breast cancer.

Materials and methods

A retrospective analysis of the literature of scientific databases Scopus, Web of Science, PubMed., MedLines for 2013-2023 was carried out.

Resulrs. Discussion

According to more than 30 years of research, it has been established that five-year adjuvant therapy with tamoxifen reduces the risk of disease recurrence by 39% [5, 6, 7, 9, 14]. Also, in patients with a widespread form of the disease, a decrease in the size of tumor foci and an increase in life expectancy can be observed [34]. However, according to some data, approximately half of patients may not have an objective response to tamoxifen therapy, and 30% may even experience disease progression against the background of tamoxifen therapy [14, 27, 39]. One of the complications of tamoxifen therapy is the increased risk of developing hyperplastic liver and endometrial processes, even in the form of adenocarcinoma, which is especially characteristic of postmenopausal patients with

ER+ breast cancer and allowed the International Agency for Research on Cancer (IARK) to classify tamoxifen as a class I carcinogen. [5, 7, 12, 17, 19, 38]. Since separate families of cytochrome P450 are involved in the metabolism of tamoxifen in the first phase, the polymorphism of their alleles, which significantly affects the activity of the corresponding enzymes and the concentration of various metabolites of tamoxifen, can partially explain these processes. The pleitropy of influencing factors significantly complicates the possibility of predicting both the therapeutic effect and complications during tamoxifen therapy, but one of the main factors is genetic polymorphisms of xenobiotic biotransformation enzymes that participate in both activation and deactivation of tamoxifen.

The cytochrome P450 (CYP) system is a multigenic superfamily of hemoproteins responsible for the metabolism of numerous xenobiotics, including therapeutic drugs, environmental chemicals and dietary components, as well as endogenous substances such as lipid-soluble vitamins, bilirubin, thyroxine, steroids, bile acids, etc. [25]. Cytochrome P450 genes encode mixed-function oxygenases (MFOs), which are responsible for the first stage of oxidative metabolism. No other enzyme system can compete for the variety of P450-metabolized substrates, ranging from low molecular weight compounds (e.g., methanol (MW=42) to large ones, such as cyclosporine A (MW=1203). In most processes biotransformation products of these reactions, as a rule, acquire reduced biological activity, and due to increased hydrophilicity, their rapid elimination occurs. But, in the case of tamoxifen, bioactive metabolites can also be formed, this is called the phenomenon of metabolic activation. States of induction or inhibition of drug-metabolizing enzymes in humans by xenobiotics underlie numerous known drug-drug interactions and are of great importance for patients receiving combined drug therapy [39]. Approximately 40% of the cytochrome P450-dependent metabolism of medicinal substances is catalyzed by polymorphic enzymes, which is the reason for individual and ethnic differences in the pharmacokinetics, pharmacodynamics and toxicity of drugs such as tamoxifen. Also, one of the most important factors affecting the activity of biotransformation enzymes is the state of hepatocyte membranes, so phenomena such as cholestatic damage to hepatocyte membranes, which can occur during intensive pharmacological therapy, have a significant negative impact on the activity of biotransformation processes [18, 39]. It should be noted that there are drugs that by themselves induce the development of cholestasis and affect the liver, they belong to different pharmacological groups: psychotropic (chlorpromazine, diazepam), antibacterial (erythromycin, nitrofurans, sulfonamides), antidepressants (carbamazepine), hypoglycemic (chlorpropamide, tolbutamide), antiarrhythmics (Aimalin), immunosuppressants (Cyclosporin A), anthelmintics (Thiabendazole), etc., and may be prescribed for the treatment of concomitant diseases or the correction of individual symptoms or conditions, which will further complicate the possibility of predicting the consequences of tamoxifen therapy [4, 7, 25, 28, 39].

The gene encoding CYP2D6 (the enzyme debrisoquine hydroxylase) is located in the long arm of chromosome 22, the length of the polypeptide chain of the protein is 497 amino acids (molecular weight - 55769). The protein coded by the gene belongs to the class of oxidoreductases, the hydroxylase subclass is involved in the metabolism of many endogenous compounds and is responsible for the metabolism of 20% of drugs, except for tamoxifen, it is involved in the biotransformation of antiarrhythmic, antihypertensive, psychotropic drugs, etc.. Currently, more than 100 are known alleles of the gene encoding CYP2D6, which determine different activity of its enzyme. Based on this, the enzymatic activity of the CYP2D6 isoform can be average in the case of alleles *1, *2, *33, *35, and reduced *9, *10, *17, *29, *41, *69, or be increased in alleles *2XN, *35X2. There are data that there are "silent" cases of activity in alleles *3, *4, * 6, *7, *8, *11-*15, *18-*21, *31, *38, *40, *42, *44 [2, 21, 33, 37].

During the first phase of metabolism of xenobiotics, tamoxifen is metabolized in several stages by cytochrome P450 enzymes, namely CYP3A4, CYP3A5, CYP1A1, CYP1A2, CYP1B1, CYP2C9, CYP2C19 and CYP2D6 isoforms. The first metabolite N-dismethyl-tamoxifen is transformed into 4-hydroxy-N-dismethyl-tamoxifen (endoxifen) under the action of CYP2D6 [1, 3, 5]. However, there are other pathways where the formation of endoxifen is catalyzed by CYP3A4/5. First, tamoxifen is converted to N-dismethyl-tamoxifen and this process is catalyzed by CYP3A4 and CYP3A5 isoforms, and many other isoforms, such as CYP1A1, CYP1A2, CYP1B1, CYP2C9, CYP2C19, and CYP2D6 enzymes, may also play a minor role in this process. Then, as mentioned above, thanks to CYP2D6, N-dismethyl-tamoxifen is converted into 4-hydroxy-N-dismethyl-tamoxifen (endoxifen) [1, 2, 23]. An alternative direction can take place under the action of CYP2B6, CYP2C9, CYP2C19 and CYP2D6 enzymes also with the formation of 4-hydroxy-tamoxifen [1, 5, 21]. Which is metabolized into endoxifen under the influence of the CYP3A4/5 isoform. Inactivation of active metabolites of tamoxifen occurs with the help of enzymes of the second phase of metabolism of xenobiotics [13]. Endoxifen and 4-hydroxy-tamoxifen, formed as a result of the phenomenon of metabolic activation by enzymes of the first phase of xenobiotic metabolism, have an affinity for estrogen receptors (ER) almost 100 times higher than that of tamoxifen and are able to suppress the proliferation of breast cancer cells almost as much more effectively [5, 7, 24]. Thus, the most active metabolites of tamoxifen: endoxifen and 4-hyroxy-tamoxifen are formed mainly due to the CYP2D6 isoform [1, 2, 21, 37]. Taking into account the above, if we take into account the ratio of the concentration of tamoxifen to the concentration of endoxifen

in the blood plasma of patients, when combining different alleles, it is possible to divide the population sample into four phenotypes according to the degree of activity of the CYP2D6 isoform: slow metabolizers (PM, have 2 alleles with missing activity), intermediate metabolizers 1 allele with normal activity or 2 with reduced activity), normal metabolizers (EM, 2 alleles with normal activity) and rapid metabolizers (UM, have double normal alleles). According to researchers, the difference in endoxifen concentrations in slow and medium (intermediate) metabolizers can reach more than 60% compared to the level of endoxifen in normal metabolizers, the median concentration in slow metabolizers compared to normal metabolizers is 5.1 ng/ml and 5.8 ng/ml, respectively [5, 7, 10, 11]. As a result of many studies, the minimum necessary threshold of endoxifen concentration was established - 5.97 ng/ml [32]. This threshold determines the expediency of prescribing tamoxifen as a representative of hormone therapy for breast cancer [10, 14, 15, 22]. Patients with concentrations below 5.97 ng/ml had a significantly increased risk of recurrence, and conversely, patients with concentrations above 5.97 ng/ml had a significantly lower risk of breast cancer recurrence and progression. There is an opinion that it is possible that the problem of slow metabolizers could be solved by increasing the dose of tamoxifen from the standard 20 mg to 40 mg, and many literary sources claim this, because only 24% of slow metabolizers had the required level of endoxifen concentration in the blood plasma [6, 35, 40]. But there are researchers who did not get similar results and there is still no single complete and clear idea about the effect of different allelic variants of CYP2D6 on the effectiveness of tamoxifen treatment [5, 7, 10, 11, 15, 16, 22, 30]. However, recently, the opinion that, taking into account the large number of cytochrome P450 isoforms involved in the complex metabolism of tamoxifen, the different individual activity of enzymes, is gaining more and more weight in literary sources of the second phase of detoxification of active metabolites of tamoxifen, it can be assumed that it is possible that not only CYP2D6 can have the main influence on the formation of active metabolites and the results of treatment, but also other enzymes of the biotransformation system of xenobiotics [1, 2, 5, 8, 11, 20, 26]. In addition, it is necessary to take into account the possible effects of drugs and endogenous metabolites of inducers and inhibitors of CYP2D6 and the state of hepatocyte membranes on the metabolism of tamoxifen [31, 36]. One should also take into account the activity of detoxification processes of xenobiotics of the second phase, including the processes of glucuronidation and sulfation, mainly catalyzed by sulfotransferase (SULT) and glucuronosyltransferase (UGT).

Conclusions and prospects for further developments

1. Taking into account the data of various experimental studies, it can be concluded that CYP2D6 can be considered a predictor of effectiveness only in patients with breast cancer (ER+) who are postmenopausal and receive 20 mg of tamoxifen per day for 5 years and do not have hepatotoxic conditions and CYP2D6 inhibition phenomena, therefore precisely in this group of patients should undergo CYP2D6 genotyping.

2. Researchers have proven that long-term tamoxifen therapy can be complicated by the development of secondary endometrial cancer. Such data gave the right to theInternational Agency for Research on Cancer(IARK) to assign tamoxifen to carcinogenic agents of class I.

3. After many experimental studies, it was proved that the unwanted effects of tamoxifen may also depend on the activity of the CYP2D6 system.

Polymorphisms of other enzymes of the biotransformation system of xenobiotics that participate in both the activation and deactivation of tamoxifen and its metabolites, both the first (CYP3A4, CYP3A5, CYP2B6, CYP2C9, CYP2C19 and CYP2D6) and the second phase (SULT and UGT), remain a promising direction for study. Research on the consequences of iatrogenic cholestasis phenomena and interactions of drugs at the level of CYP2D6 that can affect the metabolism of tamoxifen also require detailed research, taking into account the intensive pharmacotherapy of BC.

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ВПЛИВ CYP2D6 ТА ЙОГО ПОЛІМОРФНИХ ФОРМ НА МЕТАБОЛІЗМ ТАМОКСИФЕНУ ПРИ ТЕРАПІЇ ЛЮМІНАЛЬНИХ ФОРМ РАКА МОЛОЧНОЇ ЗАЛОЗИ

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Анотація. *Тамоксифен відноситься до групи селективних модуляторів естрогенових рецепторів (SERM) і метаболізується системою детоксикації ксенобіотиків причому на першій її стадії може спостерігається явище метаболічної активації. В цьому процесі безпосередньо приймає участь і CYP2D6, аналіз поліморфних форм якого може вплинути на прогноз ефективності та токсичності тамоксифену при лікуванні люмінальних форм раку молочної залози (РМЗ), що має велике значення, враховуючи термін терапії цим препаратом. Мета - проаналізувати дані наукової літератури щодо вивчення впливу CYP2D6 та його поліморфних форм на метаболізм тамоксифену при терапії люмінальних форм раку молочної залози. Проведений ретроспективний аналіз літератури наукових баз Scopus, Web of Science, PubMed., MedLines за 2013-2023 роки. Встановлено, що CYP2D6 можна вважати предиктором ефективності лікування тільки у пацієнток з РМЗ (ER+), які знаходяться в постменопаузі та отримують 20 мг тамоксифена в день 5 років і не мають гепатотоксичних станів і явищ інгібування CYP2D6, що обумовлює доцільність генотипування поліморфних варіантів CYP2D6 саме в такій групі. Тривала терапія тамоксифеном маже ускладнитися розвитком вторинного раку ендометрія. Небажані ефекти тамоксифена можуть залежати в тому числі й від активності CYP2D6. Так у повільних метаболізаторів, наприклад носіїв CYP2D6*3/*4 та CYP2D6*6/*6 спостерігалося статистично значуще збільшення частоти випадків гіперплазії ендометрія. Крім того, перспективним напрямком для вивчення залишаються поліморфізми інших ферментів системи біотрансформації ксенобіотиків, що приймають участь як в активації, так і деактивації тамоксифена та його метаболітів як першої (CYP3A4, CYP3A5, CYP2B6, CYP2C9, CYP2C19 та CYP2D6), так і другої (SULT та UGT) фази. Дослідження наслідків явищ ятрогенного холестазу та взаємодій лікарських засобів на рівні CYP2D6, що можуть впливати на метаболізм тамоксифену також потребує детального дослідження, враховуючи інтенсивну фармакотерапію РМЗ.*

Ключові слова: *тамоксифен, метаболічна активація, CYP2D6, дебризохін гідроксилаза, рак молочної залози, фармакогенетика.*