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INFLUENCE OF POLYMORPHISM OF ENZYMES OF THE UDP FAMILY-GLUCURONYL TRANSFERASES ON THE BIOTRANSFORMATION OF TAMOXIFEN IN THE THERAPY OF LUMINAL FORMS OF BREAST CANCER

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Annotation. *Tamoxifen (TAM) (1-[4-(2-dimethylaminoethoxy)-phenyl]-1,2-diphenylbut-1(Z)-ene) is a non-steroidal selective estrogen receptor modulator (SERM), which is recognized as the "gold standard" of hormone therapy for estrogen-dependent breast cancer (BC). It is known that adjuvant treatment with TAM increases recurrence-free survival and overall survival in patients with hormone-receptor-positive breast cancer. Also, tamoxifen manifests itself as a partial estrogen agonist, which can be associated with the development of complications such as endometrial cancer, venous thromboembolism, etc. The presence of resistance and relapses during TAM therapy, which reach up to 30%, remains an actual problem. Therefore, studying the mechanisms underlying the individualization of both therapeutic effect and toxicity associated with TAM remains an important challenge. In the detoxification of both TAM and its active metabolites, glucuronidation processes, which belong to the second phase of biotransformation of xenobiotics and actively take place in the liver as well as in the mammary gland, play an important role, and therefore the study of this process can contribute to the understanding of the interindividual variability of the therapeutic effect and toxicity of TAM. The aim - to analyze the data of the scientific literature on the study of the influence of glucuronyltransferase (UGT) enzymes and their polymorphic forms on the biotransformation of TAM and its active metabolites in the treatment of hormone-receptor-positive 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 possible to draw the following conclusions that UGT isozymes are responsible for the conjugation and detoxification of tamoxifen and its metabolites in the form of glucuronides 4-OH-tamoxifen-N-glucuronide, 4-OH-tamoxifen-O-glucuronide and endoxifen-O-glucuronide. UGT1A8, UGT1A10, UGT2B7, UGT2B15 and UGT2B17 isoforms played the greatest role in glucuronidation of tamoxifen and its active metabolites, but UGT1A4 was recognized as the main one. Depending on the content of active TAM metabolites and their glucuronides in the blood plasma, it can be stated that carriers of the UGT2B15 Lys523Thr and UGT2B17del alleles demonstrated increased enzyme activity, and individuals with one variant UGT2B15 523Thr allele can even be considered superactive metabolizers of 4-OH-tamoxifen-O- glucuronide and endoxifen-glucuronide. Also, high levels of 4-OH-tamoxifen-N-glucuronide were observed in carriers of the allele of the UGT2B17del genotype. Carriers of the above alleles have high activity of glucuronidation processes and low levels of active metabolites of TAM, which calls into question the rationality of prescribing TAM as hormone therapy. In contrast, patients with UGT1A4 48Val, UGT2B7 268Tyr alleles, or with wild-type genotypes for UGT2B17 nodel and UGT2B15 523Lys, will have high levels of active metabolites and are the group of choice for tamoxifen therapy in estrogen-receptor-positive breast cancer because they will have a low rate of glucuronidation and detoxification. However, in order to create a system of clinical algorithms for the formation of tamoxifen-sensitive groups of patients, further detailed study of other possibilities of the biotransformation system in the metabolism of tamoxifen is required.*

Keywords: *tamoxifen (TAM); biotransformation, UDP-glucuronyltransferase (UGT), breast cancer; pharmacogenetics.*

Introduction

Breast cancer (BC) is a major medical, social and ethical problem. Every minute, up to 3 cases of breast cancer are registered in the world, and unfortunately, more than one thousand people die from this pathology. In Ukraine, over the past 20 years, the number of cases of breast cancer has increased by almost 2.8 times, and the morbidity and mortality rates from breast cancer are much higher compared to other countries of the world by 45% and 56%, respectively. Of great importance in the treatment of this disease is hormone therapy, the "gold standard" of which is tamoxifen, which belongs to selective estrogen receptor modulators (SERMs). But the complexity of predicting therapeutic and toxic effects against the background of a significant percentage of resistance in patients requires a detailed understanding of all processes of TAM metabolism. The therapeutic effect of TAM therapy is determined precisely by its active metabolites formed after the first phase of biotransformation of xenobiotics. In the detoxification of active metabolites, an important role is played by the system of glucuronyltransferase enzymes, which is one of the most powerful in the second phase of metabolism of xenobiotics and can significantly affect the rate of detoxification and, accordingly, the therapeutic effect of TAM.

The aim - to analyze the data of the scientific literature on the study of the influence of glucuronyltransferase (UGT) enzymes and their polymorphic forms on the biotransformation of TAM and its active metabolites in the treatment of hormone-receptor-positive 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.

Results. Discussion

The main ways of detoxification and elimination of TAM and its active metabolites are conjugation reactions of the second phase of xenobiotic metabolism, such as sulfation and glucuronidation (the process occurs due to the conjugation of TAM and its active metabolites with glucuronic acid) [1, 2, 6, 7, 9]. TAM and 4-OH-TAM undergo N-glucuronidation, while O-glucuronidation is characteristic of 4-OH-TAM and endoxifen [2, 7, 22, 28]. These TAM glucuronide conjugates were determined by researchers in the urine and plasma of patients with breast cancer who received TAM endocrinotherapy [6, 7, 28].

The human *UGT1* and *UGT2* gene families are known to encode 19 transcripts that have been identified in many tissues. UGT1 isoforms are encoded by one gene locus on chromosome 2-q37 [7, 12, 23]. Thus, UGT1A isoforms have more than 50% sequence homology with each other, but less than 50% identity with members of the 2B family. UGT1A isoforms are synthesized by alternative splicing of a unique exon 1 to common exons 2-5. Approximately two-thirds of the lumenal domains of the proteins are encoded by the *UGT1A* locus. The structure of the enzyme is encoded by the first nine functional exon "cassettes" (*UGT1A1* and *UGT1A3-10*) and three non-functional exon 1 sequences (*UGT1A2*, *UGT1A11*, and *UGT1A12*), which encode unique N-terminal domains. Common exons 2-5 encode a UDP-glucuronic acid (UDP-GA) binding site and the remainder of the lumenal domain, which is identical in all UGT1A family members [12, 23, 29]. The human *UGT2* gene family is divided into two subfamilies, *UGT2A* and *UGT2B*. In contrast to the *UGT1* family, most *UGT2* genes are represented by six exons that are not shared among *UGT2* family members. *UGT2* genes are located on chromosome 4-q13. Much attention to the study of the *UGT2* family is due to the number of isoforms of the UGT2B subfamily [28, 30,].

Polymorphic variations of the coding region of *UGT* genes are associated with changes in both UGT expression and enzyme activity, which can significantly affect the processes of glucuronidation of endo- and exogenous xenobiotics [15, 25]. It was shown that among the many UGT isoforms involved in TAM detoxification (including UGT1A8, UGT1A10, and UGT2B7), UGT1A4 was identified as the main UGT isoform involved in the glucuronidation of TAM and its metabolites. UGT2B7 demonstrated the highest affinity and activity for trans-4-hydroxytamoxifen [26, 16, 30]. The *UGT1A4* gene encodes an enzyme that catalyzes the formation of a glucuronide bound by quaternary ammonium to TAM [4, 7, 8, 18]. Two unlinked m issense polymorphisms were identified in this gene: in codon 24 Pro>Thr (rs6755571) and in codon 48 Leu>Val (rs2011425). Individuals homozygous for *UGT1A4* 48VAL demonstrated significantly lower mean concentrations of both TAM glucuronide metabolites compared to individuals with the wt/wt plus wt/48Val genotype. The effect of the above-mentioned polymorphisms on the speed of the enzymatic reaction also depends on which of the TAM metabolites undergoes glucuronidation [18].

At the same time, there are contradictory, ambivalent results. Data from in vitro studies indicate similar rates of glucuronidation of TAM as a substrate in the presence of both polymorphic alleles (*UGT1A4* 24Thr and *UGT1A4* 48Val) as well as by the wild-type enzyme [32]. This was confirmed by the absence of differences in the concentrations of TAM metabolites between the two *UGT1A4* genotypes (SNP *UGT1A4* 24 Thr and *UGT1A4* 48 Val) in the blood plasma of patients [33]. However, individuals homozygous for *UGT1A4* 48 Val had significantly lower mean concentrations of 4-OH-TAM-O-Gluc and endoxifen-Gluc than wt/wt plus wt/48Val subjects. Low activity of trans-4-hydroxytamoxifen glucuronidation was also observed in carriers of the *UGT1A4* 24Thr/48Leu allele [4, 8, 18].

Data from numerous experimental studies indicate that glucuronidation activity for the trans-isomers of 4-hydroxytamoxifen or endoxifen is not detected in individuals with the *UGT1A8* allele, 173Ala/277Tyr, while glucuronidation activity for TAM in carriers of the *UGT1A8* 173Gly/ Allele 277Cys or *UGT1A10* 139Lys did not change compared to the values of wild-type carriers. UGT2B7 is the main liver enzyme responsible for O-glucuronidation of trans-isomers of 4-OH-TAM and endoxifen [2, 7]. In various studies of the enzyme UGT2B7, which is located in the epithelium lining the ducts of the mammary glands, significant individual variability in its activity has been shown. There are different data on the activity of glucuronidation in the case of a missense polymorphism of the *UGT2B7* gene in which the amino acid tyrosine replaces histidine at position 268 (rs 7439366) [7, 10]. Some authors did not obtain a correlation between the concentrations of endoxifen or 4-OH-TAM in blood plasma in carriers of the *UGT2B7* 268Tyr allele [2, 28], in contrast to others, who claim a significant tendency to decrease 4-OH-TAM O-glucuronidation with an increase in the number allele UGT2B7 268Tyr. Individuals homozygous for the *UGT2B7* 268Tyr allele showed average substrate/product ratios for 4-OH-tamoxifen/4-OH-tamoxifen-O-glucuronide and 4-OH-tamoxifen/4-OH-tamoxifen-N-glucuronide, indicating reduced activity glucuronidase in contrast to wild-type homozygotes or polymorphism heterozygotes. However, carriers of the *UGT2B7* 268Tyr allele showed a decrease in glucuronidation activity for the trans-isomers of 4-hydroxytamoxifen and endoxifen compared to wild-type *UGT2B7* 268His [2, 31, 34]. Carriers of the wild-type *UGT2B7* 268His allele showed significantly higher glucuronidation activity to trans-4-hydroxytamoxifen and trans-endoxifene compared to the *UGT2B7* 268Tyr variant.

The UGT2B15 isoform was originally identified as a potent androgen steroid glucuronidator. However, its participation in the metabolism of not only endo but also exogenous xenobiotics has been shown [5, 21, 31]. Two non-synonymous polymorphisms in the *UGT2B15* gene, Asp85Tyr (rs1902023) and Lys523Thr (rs4148269), most likely have little effect on the detoxification of TAM and its active metabolites, although there are data on studies of carriers of the Lys523Thr *UGT2B15* polymorphism, which indicate changes in the glucuronidation activity of TAM itself in carriers of this polymorphism [5, 21, 30, 31]. The authors claim that carriers of the *UGT2B15* Lys523Thr and *UGT2B17*del alleles are associated with a possible increase in enzyme activity and substantiate their data by the fact that the main hepatic isoform of UGT2B17 carries more than 95% of the amino acid sequences in common with UGT2B15 and has a similar substrate specificity. Such a high sequence identity between *UGT2B15* and *UGT2B17* suggests that the genes arose as a result of duplication. Thus, patients with one variant allele of *UGT2B15* 523Thr demonstrated significantly higher levels of 4-OH-tamoxifen-O-glucuronide and endoxifen-glucuronide, possibly indicating the effect of variation in the number of gene copies [5, 21, 31].

Also, high levels of 4-OH-tamoxifen-N-glucuronide were observed in the blood plasma of *UGT2B17*del genotype carriers, which can be attributed to a mechanism that compensates for the higher expression of other genes in *UGT2B17* del/del carriers [30]. In addition, studies have shown that the activity of UGT1A10 and UGT2B7 was reduced in malignant breast tumors compared with the corresponding enzymes in normal breast tissues [7, 10, 27, 20]. Also, the glucuronidation activity of estradiol, the most physiologically active form of estrogen, was reduced in most cases of breast cancer compared to normal breast tissue [11, 14, 27].

For quite a long time, studies of TAM metabolism features were focused on the role played by genetic changes in biotransformation system enzymes (insertions, deletions, and mutations) that affect their activity and/or expression [14]. However, it is now recognized that epigenetic mechanisms also play an important role in the functioning of TAM metabolism enzymes [24]. One of the main epigenetic mechanisms is DNA methylation. DNA hypermethylation of CpG-rich regions (also known as CpG islands) located in the promoter region of many genes of biotransformation enzymes also leads to changes in their expression and activity. Studies are currently underway to determine whether DNA methylation can be used to predict the therapeutic efficacy of TAM. Changes in the regulation of UGT activity due to methylation led to suppression of *UGT1A1* expression [3, 17, 19, 28,]. It is possible that this way of influencing UGT activity can significantly change the content of TAM and its active metabolites in cases of fast and super-fast metabolizers. The study of the complex regulation of UGT activity, including epigenetic and genetic factors, the influence of inducers and inhibitors, the role of genes of the third phase of xenobiotic metabolism, will help to maximally individualize TAM therapy with the possibility of predicting both therapeutic and toxic effects.

Conclusions

1. It is possible to draw the following conclusions that UGT isozymes are responsible for the conjugation and detoxification of tamoxifen and its metabolites in the form of glucuronides 4-OH-tamoxifen-N-glucuronide, 4-OH-tamoxifen-O-glucuronide and endoxifen-O-glucuronide. UGT1A8, UGT1A10, UGT2B7, UGT2B15 and UGT2B17 isoforms played the greatest role in glucuronidation of tamoxifen and its active metabolites, but UGT1A4 was recognized as the main one. Depending on the content of active TAM metabolites and their glucuronides in the blood plasma, it can be stated that carriers of the *UGT2B15* Lys523Thr and *UGT2B17del* alleles demonstrated increased enzyme activity, and individuals with one variant *UGT2B15* 523Thr allele can even be considered superactive metabolizers of 4-OH-tamoxifen-O- glucuronide and endoxifen-glucuronide.

2. Also, high levels of 4-OH-tamoxifen-N-glucuronide were observed in carriers of the allele of the *UGT2B17del* genotype. Carriers of the above alleles have high activity of glucuronidation processes and low levels of active metabolites of TAM, which calls into question the rationality of prescribing TAM as hormone therapy. In contrast, patients with *UGT1A4* 48Val, *UGT2B7* 268Tyr alleles, or with wild-type genotypes for *UGT2B17* nodel and *UGT2B15* 523Lys, will have high levels of active metabolites and are the group of choice for tamoxifen therapy in estrogen-receptor-positive breast cancer because they will have a low rate of glucuronidation and detoxification.

However, in order to create a system of clinical algorithms for the formation of tamoxifen-sensitive groups of patients, further detailed study of other possibilities of the biotransformation system in the metabolism of tamoxifen is required.

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ВПЛИВ ПОЛІМОРФІЗМІВ ФЕРМЕНТІВ РОДИНИ УДФ-ГЛЮКУРОНІЛТРАНСФЕРАЗ НА БІОТРАНСФОРМАЦІЮ ТАМОКСИФЕНУ ПРИ ТЕРАПІЇ ЛЮМІНАЛЬНИХ ФОРМ РАКА МОЛОЧНОЇ ЗАЛОЗИ

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Анотація. *Тамоксифен (ТАМ) (1- [4-(2-диметиламіноетокси)-феніл]-1,2- дифенілбут-1(Z)-ен) це нестероїдний селективний модулятор естрогенових рецепторів (SERM), який визнаний "золотим стандартом" гормонотерапії естрогензалежного раку молочної залози (РМЗ). Відомо, що ад'ювантне лікування ТАМ збільшує безрецидивну виживаність і загальну виживаність у пацієнток з гормонально-рецептор-позитивним РМЗ. Також тамоксифен проявляє себе і як частковий естроген-агоніст, що може бути пов'язано з розвитком ускладнень таких як рак ендометрію, венозна тромбоемболія та ін. Актуальною проблемою лишається наявність резистентності та рецидівів при терапії ТАМ, які сягають до 30%. Тому вивчення механізмів, що лежать в основі індивідуалізації як лікувального ефекта так і токсичності, пов'язаної з ТАМ, залишається важливою проблемою. В детоксикації як ТАМ, так і його активних метаболітів велику роль грають процеси глюкуронізації, які відносяться до другої фази біотрансформації ксенобіотиків і активно проходять в печінці, а також в молочній залозі і тому вивчення цього процесу може сприяти розумінню міжіндивідуальної мінливості лікувального ефекту і токсичності ТАМ. Мета - проаналізувати дані наукової літератури щодо вивчення впливу ферментів глюкуроніltрансферз (UGT) та їх поліморфних форм на біотрансформацію ТАМ та його активних метаболітів при терапії гормонально-рецептор-позитивного РМЗ. Проведений ретроспективний аналіз літератури наукових баз Scopus, Web of Science, PubMed., MedLines за 2013 - 2023 роки. Можливо зробити наступні висновки, що ізоферменти UGT відповідальні за кон'югацію та детоксикацію тамоксифену та його метаболітів у вигляді глюкуронідів 4-ОН-тамоксифен-N-глюкуроніду, 4-ОН-тамоксифен-О-глюкуроніду і ендоксифен-О-глюкуроніду. Найбільшу роль в глюкуронізації тамоксифену та його активних метаболітів мали ізоформи UGT1A8, UGT1A10, UGT2B7, UGT2B15 т UGT2B17, але основною було визнано UGT1A4. В залежності від вмісту в плазмі крові активних метаболітів ТАМ та їх глюкуронідів можно стверджувати, що носії алелів UGT2B15 Lys523Thr та UGT2B17del продемонстрували підвищену активність ферменту, а особи з одним варіантним алелем UGT2B15 523Thr можно навіть вважати супер активними метаболізаторами по 4-ОН-тамоксифен-О-глюкуроніду та ендоксифен-глюкуроніду. Також високі рівні 4-ОН-тамоксифен-N-глюкуроніду спостерігалися у носіїв алелю UGT2B17del генотипу. Особи носії вищевказаних алелів мають високу активність процесів глюкуронізації і низьки рівні активних метаболітів ТАМ, що ставить під сумнів раціональність призначення ТАМ у якості гормонотерапії. Навпаки, пацієнти з алелями UGT1A4 48Val, UGT2B7 268Tyr або з генотипами дикого типа для UGT2B17 nodel та UGT2B15 523Lys, будуть мати високі рівні активних метаболітів і є групою вибору для терапії тамоксифеном естроген -рецептор -позитивного раку молочної залози, оскільки будуть мати низьку швидкість глюкуронідації і детоксикації. Однак для створення системи клінічних алгоритмів по формуванню тамоксифен чутливих груп пацієнтів потрібно подальше детальне вивчення і інших можливостей системи біотрансформації в метаболізмі тамоксифена.*

Ключові слова: *тамоксифен (ТАМ), біотрансформація, УДФ- глюкуроніltрансфераза (UGT), рак молочної залози; фармакогенетика.*