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Integrating Personalization of Treatment with Tamoxifen into Pharmacy Practice Via Clinical Pharmacist Role in Therapy Management

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Abstract

The concept of individualized therapy is intended to deliver the right therapy to the right patient at the right time. Personalization of treatment aims to shift health care from population based or empirical approach to scientifically tailored approach. Pharmacogenenetics use the genetic information such as DNA sequence, gene expression and copy number to explain the inter-individual differences in drug metabolism (pharmacokinetics) and physiological drug response (pharmacodynamics), to predict the efficacy and toxicity of drugs and to identify responders and non responders to a specific drug. Success of the personalized medicine depends on the identification of predictive biomarkers and development of accurate and reliable diagnostics.

Tamoxifen is estrogen receptor antagonist. It is the corner stone therapy for breast cancer either in the adjuvant or metastatic setting mainly in patients with female hormone receptors positivity. Response to tamoxifen is affected by the genetic variation of CYP2D6. This cytochrome is responsible for tamoxifen metabolism to its active metabolite endoxifen. There is still no recommendation on the clinical utility of CYP2D6 genotype as biomarker to predict the treatment clinical outcomes in breast cancer patients. The reported data suggest that polymorphisms in CYP2D6 and ER genotype might be useful in selecting women who would gain the highest benefit from tamoxifen and those who are susceptible to adverse effects. For the time being the optimal strategy for individualization of tamoxifen therapy is likely to be the therapeutic drug monitoring.

Pharmacists have a distinct knowledge and background about medications and have the ability to develop and lead pharmacogenetic programs. they have a fundamental responsibility and accountability to advocate for the importance and rational for implementation of pharmacogenetic testing, to set recommendations to optimize medication therapy based on test results, to conduct and participate in research that accelerate the application of pharmacogenetics to clinical practice and to educate health care professionals and patients. Given the uncertainties in this field management decision should be individual and based on patient possible risk, alternatives, preferences and the best available evidence.

Keywords: Pharmacology; Tamoxifen; Estrogen

Tamoxifen pharmacology

Tamoxifen is a hormone therapy belongs to the selective estrogen receptor modulators (SERMs) class of therapy. This drug class has both estrogenic and antiestrogenic effects. It acts as an estrogen (stimulating agent) in endometrium cell proliferation, cholesterol metabolism and bone density and acts as anti-estrogen (inhibiting agent) in the mammary tissue such as breast. Tamoxifen is a nonsteroidal drug that binds to estrogen receptors (ER) and lead to change or blockage in the estrogen dependent genes expression. The binding of tamoxifen to the nuclear chromatin for a long time results in reduction of DNA polymerase activity, impairment in thymidine utilization, blockage in ER-alpha or ER-beta receptors leading to both estrogenic and antiestrogenic effects [1,2].

Tamoxifen pharmacokinetics

Absorption and distribution: Tamoxifen is available as 10mg tablet and administered as 20mg once daily. The average peak plasma concentration of a range of 35 to 45 ng/ml occurs about 5 hours after administration of 20mg single oral dose. The reduction in tamoxifen plasma concentration is biphasic with a terminal half life of about 5-7 days. The steady state concentrations of tamoxifen are achieved in about 4 weeks after initiation of therapy and the steady state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks. The suggested half life for the metabolite is 14 days [1,2].

Metabolism: Tamoxifen is extensively metabolized hepatically after oral administration. The major metabolite for tamoxifen found in plasma is N-Desmethyl – tamoxifen. The activity of this metabolite is similar to tamoxifen. 4-hydroxy- tamoxifen is a minor metabolite for tamoxifen found in plasma. 4-hydroxy – tamoxifen formation is catalyzed mainly by cytochrome P450 (CYP) 2D6, and also by CYP2C9 and 3A4. 4-Hydroxy –tamoxifen possesses 30 to 100 times greater affinity for the estrogen receptor and 30 to 100 times greater potency at inhibiting estrogen-dependent cell proliferation compared to tamoxifen. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein [1,2].

Excretion: The primary route of elimination of tamoxifen is fecal excretion. About 65% of the administered dose excreted from the body over 2 weeks. Tamoxifen is excreted mainly as polar conjucates, with

unchanged drug and unconjucated metabolites accounting for less than 30% of the total fecal radioactivity [1,2].

Tamoxifen therapeutic indications

Tamoxifen works to prevent tumors known to be responsive to female hormones as estrogen and progesterone. This kind of tumor could be identified by the presence of hormone receptors. Tumors then are called either estrogen receptor positive or progesterone receptor positive. Tamoxifen is antineoplastic agent, estrogen receptor antagonist and selective estrogen receptor (ER) modulator. It is approved by FDA for treatment of metastatic breast cancer in pre and postmenopausal women, and as adjuvant therapy with surgery and radiation to reduce the risk of invasive breast cancer and to reduce the incidence of breast cancer in high risk women. Tamoxifen is used for more than 30 years to treat hormone receptor positive breast cancer. Its standard of care therapy in premenopausal women is a 5 year treatment [3-5].

Early Breast Cancer Trialists‟ Collaborative Group (EBCTCG) reported data for meta-analysis of individual patients from 20 trials (n=21,457) in early breast cancer. They compared treatment of 5 years of tamoxifen versus no adjuvant tamoxifen. Breast cancer mortality was reduced by about a third throughout the first 15 years; $P < 0.0001$. ER status was the only important predictive value of the proportional risk reduction [6,7].

Consept of individualized therapy

The concept of personalized health care (PHC) has attracted scientists and policy makers. Michael O. Leavitt defined PHC as „the combination of basic scientific breakthroughs of the human genome with computer-age ability to exchange and manage data‟. Completion of human genome created knowledge that enabled researchers to identify and characterize variations in individual patients‟ biology. Gene based medicine help create more effective therapy for subpopulations. It is currently applied in practice [8].

The personalized health care has a potential to sharpen the health care focus and improve its effectiveness and efficiency. Personalized therapy aims to shift health care to scientifically informed and tailored approach for individual patients rather than population based or empirical approach. It is intended to deliver the right therapy to the right patient at the right time [9].

Clinicians observed that patients might have similar symptoms but have different illness related to different causes. At the same time medical interventions might work in some patients and not in others with the same disease. Variability in response of patients to certain drugs might lead to difficulty to predict who will benefit from a medication and who will not respond and who will experience side effects. Scientists tried to understand through studying pharmacogenomics / pharmacogenetics how difference in gene and its expression affect individuals‟ response to therapy.

Pharmacogenetics use the genetic information such as DNA sequence, gene expression and copy number to explain the inter-individual differences in drug metabolism (pharmacokinetics) and physiological drug response (pharmacodynamics), predict the efficacy and toxicity of drugs and identify responders and non responders to a specific drug. Success of the personalized medicine depends on the identification of predictive biomarkers and development of accurate and reliable diagnostics [10].

In 1980s breakthroughs in molecular characterizations of different diseases and mainly cancer introduced promising possibilities in tailoring therapy to clinically match specific disease characteristics and individual clinical situation. Trastuzumab was developed and approved in 1998 as important discovery about the role of cell growth and oncogenes. It is the genetically guided therapy for treatment of metastatic breast cancer with over expression of HER2 [10].

Tamoxifen was discovered even earlier than Trastuzumab. In late 1970s tamoxifen was developed as the first targeted therapy for breast cancer. It was genetically guided for the treatment in the neoadjuvant, adjuvant and metastatic breast cancer settings with hormone receptor positivity, estrogen and progesterone receptors [11].

Pharmacogenetics has a potential to identify the right drug and dose for each patient through studying the role of inheritance in the individual variation in drug response. Individuals‟ differences in drug response, drug efficacy and the likelihood of side effects might be related to many factors as age, sex, disease, drug interaction and genetic factors. Pharmacogenetics are potentially contributed in medical practice, every pathway of drug metabolism will eventually have genetic variation [12-13].

Different steps involved in the pharmacokinetics and pharmacodynamics process of a drug. This process starts with drug administration, absorption, and distribution to its site of action such as receptors and enzymes, followed by metabolism then excretion. Each of these processes could potentially involve clinically significant genetic variation. Scientists started to understand the inherited trait after identification of the enzymes responsible for drug metabolism; the genes encoded the protein and the DNA sequence variation within the gene. Most of the pharmacogenetic traits were due to genetic polymorphism [14-16].

Pharmacogenetics / pharmacogenomics of Tamoxifen

Many agents have been practically tested for treatment of breast cancer either in metastatic or adjuvant settings since 1980s leading to significant reduction in 5 years recurrence as well as 15 year mortality rates despite the increase in breast cancer prevalence. Clinicians noticed that benefit from identical systemic therapies might differ in individual women due to difference in tumor characteristics. For example in case of hormonal treatment with tamoxifen in breast cancer patients, expression of estrogen and progesterone receptors are essential but around 50% of women with hormonal receptors positive will benefit from hormonal treatment [16-18].

Tamoxifen interindividual variation

Each gene encodes for CYP450 enzymes has a known genetic polymorphisms that affect its catalytic activity. For example in case of tamoxifen single nucleotide polymorphism in CYP 2D6 genes can lead to complete lack of enzymatic activity due to the formation of truncated inactive proteins [19-26].

Scientists identified over 80 different CYP2D6 alleles and their frequencies variation among ethnic groups. The null allele CYP2D6*4 is the most common variant allele in Caucasians, whereas CYP2D6*10 is most common in Asian populations. Patients can be classified based on allele combinations or duplication into four major genotypes: Poor metabolizers presents (homozygous for null alleles), intermediate metabolizers (heterozygous for null or partially functional alleles), extensive metabolizers (homozygous for wildtype alleles), and

ultrarapid metabolizers (carrying more than two CYP2D6 copies in their genome) [22-27].

Effect of CYP2D6 inhibitors

The enzymatic activities of CYP2D6 can be affected not only by the presence of various polymorphisms but also due to intake of many drugs. Examples for strong CYP2D6 inhibitors are fluoxetine, paroxetine and quinidine, moderate inhibitors are steraline, duloxetine, diphenhydramine, cimetidine and amiodarone. Other drug interactions can be found at www.drug-interactions.com

Association between CYP2D6 genotype and patient outcomes

The investigators from the Consortium on Breast Cancer Pharmacogenomics conducted a prospective study including 300 women started tamoxifen for treatment or prevention of breast cancer in the adjuvant setting. Data analysis revealed that women with one or two null CYP2D6 alleles had significantly lower endoxifen plasma concentration compared with women with normal CYP2D6. At the same time the plasma level of endoxifen concentration will be reduced similar to that seen in patients with two null alleles in case of concomitant administration of strong inhibitors of CYP2D6 as paroxetine. The data show that the CYP2D6 activity is the major determinant of plasma concentration of endoxifen. Attempts have been made to validate CYP2D6 genotype as a biomarker for prediction of response and long outcomes of tamoxifen treated women [28-30].

The North Central Cancer Treatment Group randomized Phase III trial was designed to test the value of adding 1 year of fluoxymesterone to 5 years of adjuvant tamoxifen therapy. The primary objectives were to determine the relationship between genotype and relapse free time, disease free survival and overall survival. The recurrence free survival and disease free survival were significantly worse in women who were poor metabolizers with the CYP2D6*4 genotype but not the overall survival compared to the intermediate or extensive metabolizers [31-32].

A second study analyzed the impact of CYP2D6 inhibitors and tamoxifen adherence in 1900 breast cancer patients from Dutch Medical Register. Results revealed that patients on concomitant moderate or strong CYP2D6 inhibitor and tamoxifen had the same event free survival as patients did not use inhibitor. While reduced tamoxifen adherence below 90% was correlated with reduced event free survival (EFS). No definitive conclusions was drawn regarding using CYP2D6 inhibitor and breast cancer outcomes, but it appears that utilization of weak CYP2D6 inhibitors is safe in patients treated with tamoxifen [33-34].

Level of evidence

The level of evidence of the impact of tamoxifen metabolism on breast cancer outcomes is still preliminary as most of the evidence come from retrospective studies of small to moderately sized cohort studies. This increases the chance for false positive or biased results. The evidence in this field is still evolving, the correlation between endoxifen level and CYP2D6 genotype and patient outcomes has not demonstrated clearly in prospective studies.

It is wise to avoid moderate to strong CYP2D6 inhibitors for patients receiving tamoxifen at the same time especially if there is effective alternatives. For example use of citalopram for hot flushes or depression, it seems reasonable for patient safety. This will minimize the risk of potential drug interaction that might affect patient outcome. Overall, data reported suggest that polymorphisms in CYP2D6 and ER genotype might be useful in selecting women who would gain the highest benefit from tamoxifen and those who are susceptible to adverse effects. Given the uncertainties in this field management decision should be individual and based on patient possible risk, alternatives, preferences and the best available evidence [35-37].

Role of Pharmacist in pharmacogenetics

Clinical pharmacists are considered as key member in the multidisciplinary team. They possess a distinct knowledge and background about medications and have excellent skills and abilities that make them uniquely positioned to lead inter professional efforts. They have the ability to develop and order pharmacogenetic tests, interpret test results then report to authority people. Clinical pharmacists therefore have a fundamental responsibility and accountability to ensure performing pharmacogenetic tests when needed to optimize medication safety [38-40].

Pharmacogenetic testing can improve drug related outcomes. For example more appropriate selection of medications, decrease the duration of treatment, improve adherence to medication, enhance patient safety, decrease treatment cost, and minimize the suboptimal clinical outcomes [41].

The American Society of Health System Pharmacists (ASHP) believes and supports the leadership role of pharmacists in the application of pharmacogenetics. Pharmacists should have a basic understanding of pharmacogenomics to provide appropriate patient care recommendations. Pharmacists can work collaboratively with the prescriber and the lab, review all patients prescribed medications and the genomic data and then to offer assessment and to set recommendations for the best fit for individual patient [39-41].

A list of drugs for which the pharmacogenomic markers are involved in the drug labeling is provided by FDA. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published ASHP endorsed therapeutic guidelines for multiple drug-gene pairs [42-45].

Pharmacists responsibilities for pharmacogenetics include educating health care professionals, patients and publics, promote the optimal use and the appropriate timing for the test, interpret the test results, advocate for the importance and rational for implementation of pharmacogenetic testing, set recommendations to optimize medication therapy based on test results, conduct and participate in research that accelerate the application of pharmacogenetics to clinical practice.

Conclusion

Tamoxifen is the corner stone treatment in hormone receptor positive breast cancer patients either in the adjuvant or metastatic settings. Individualization of tamoxifen therapy based on patients pharmacogenetics data profile help treatment optimization, improve patients'' clinical outcomes, minimize toxicities, reduce treatment cost and enhance quality of life. Clinical pharmacists are the drug therapy experts and specialists. They have a unique leadership position to apply and implement pharmacogenetics in clinical practice. This emerging science should be spearheaded by pharmacists in hospitals and institutions to promote safe, effective and cost-efficient therapeutic practices.

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