REVIEW

Pharmacogenomic approaches in the treatment of breast cancer by tamoxifen

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Abstract: Breast cancer (BC) is a highly diverse complaint rather than sole disease consisting of several markers linked to typical features of tissues, medical assessment and reaction to treatment. Mutation in RAS/MEK/ERK and PI3K-AKT-mTOR pathway is involved in pathogenesis of BC. Application of pharmacogenomics will lead to individualization of therapy, which is totally contrast to nowadays clinical practice, in which drug's effects are studied on large group of patient regardless of their genetic based difference. The genetic differences in persons affect the therapeutic action and concentration of Tamoxifen in each individual. Therefore, it is, concluded to choose best drug regimen for each patient on individual basis and to circumvent the patient by toxic effect of drug.

Keywords: Breast cancer, tamoxifen, pharmacogenomics.

Breast cancer (BC) is a highly diverse complaint rather than sole disease (Polyak, 2007) consisting of several markers (Qadir and Malik, 2008) linked to typical features of tissues, medical assessment and reaction to treatment (Weigelt *et al.,* 2010). Different advanced techniques have publicized 5 main molecular subtypes of BC: basal-like, luminal A, luminal B, Humen epidermal growth factor receptor positive (HER2+)/estrogen receptor negative (ER–), and normal breast-like (Polyak, 2007). BC is treated by various approaches such as surgical excision, radiotherapy, hormonal blocking therapy and use of chemotherapeutic agents (Lukaszewicz *et al.,* 2010).

Risk factors for breast cancer

Alcoholic intake (Năsui *et al.,* 2009), Dichloro-diphenyl-dichloro-ethylene (a metabolic product of the DDT) contact can boost up the peril (Snedeker, 2001), being deficient of lactation (Gajalakshmi *et al.,* 2009; Shantakumar *et al.,* 2007). Diet has also an impact on BC (Wang *et al.,* 2008). Nicotine use or cigarettes (De Silva *et al.,* 2010), relatives having BC, having any other breast ailments (Velentgas and Daling, 1994) are the three major risk factors. Oral contraceptives have found to vaguely amplify a females's peril for BC (Ursin *et al.,* 1998).

Pathogenesis of breast cancer

The Ras/MEK/ERK and PI3K/AKT mechanisms impart their part in the conduction of signal, starting by growth factor receptors, to control and escape the programmed cell death. Abnormal expression or mutation in the members of above mentioned mechanisms, is responsible for proliferation of tumor cells (Mazzarino *et al.,* 2006). Fig. 1 explains these mechanisms. Mutation in RAS/MEK/ERK and PI3K-AKT-mTOR pathway is involved in pathogenesis of BC. PI3K-AKT-mTOR is chief signaling mechanism, which play a significant role in carcinogenesis. mTOR is a chief kinase that control neoplastic cell propagation, development, endurance and development of new blood vessels. Cancer cells break away from usual mechanism which maintains the stability among cell death and endurance. PI3K-AKT-mTOR is a promoter for endurance through embarrassment of proapoptotic factors and inauguration of anti-apoptotic factors. By addition of phosphate group, PI3K-AKT-mTOR hamper the action of proapoptotic factors whereas trigger the action of anti-apoptotic factors. Cell has PTEN (phosphatase/tensin) phosphatase to block this pathway. Declines in PTEN function circuitously inaugurate PI3K-AKT-mTOR action thus playing a part in carcinogenesis. RAS/MEK/ERK is a signal transduction pathway, mutation in the gene of these pathway will lead to inability of cell to death by apoptosis.

Mutated PTEN (phosphatase/tensin homolog deleted on chromosome 10) is thought to act via the presumed PI3K-AKT-mTOR signal transduction mechanism. Particularly, failure of PTEN leads to activation of AKT, which sequentially activates the mechanisms that inhibit programmed cell death, leading to cancer proliferations (Panigrahi *et al.,* 2004).

Mutated PTEN can also inhibit the Raf/MEK/ERK signal transduction mechanisms by activated Akt which causes inactivation and phosphorylation of Raf (McCubrey *et al.,* 2007).

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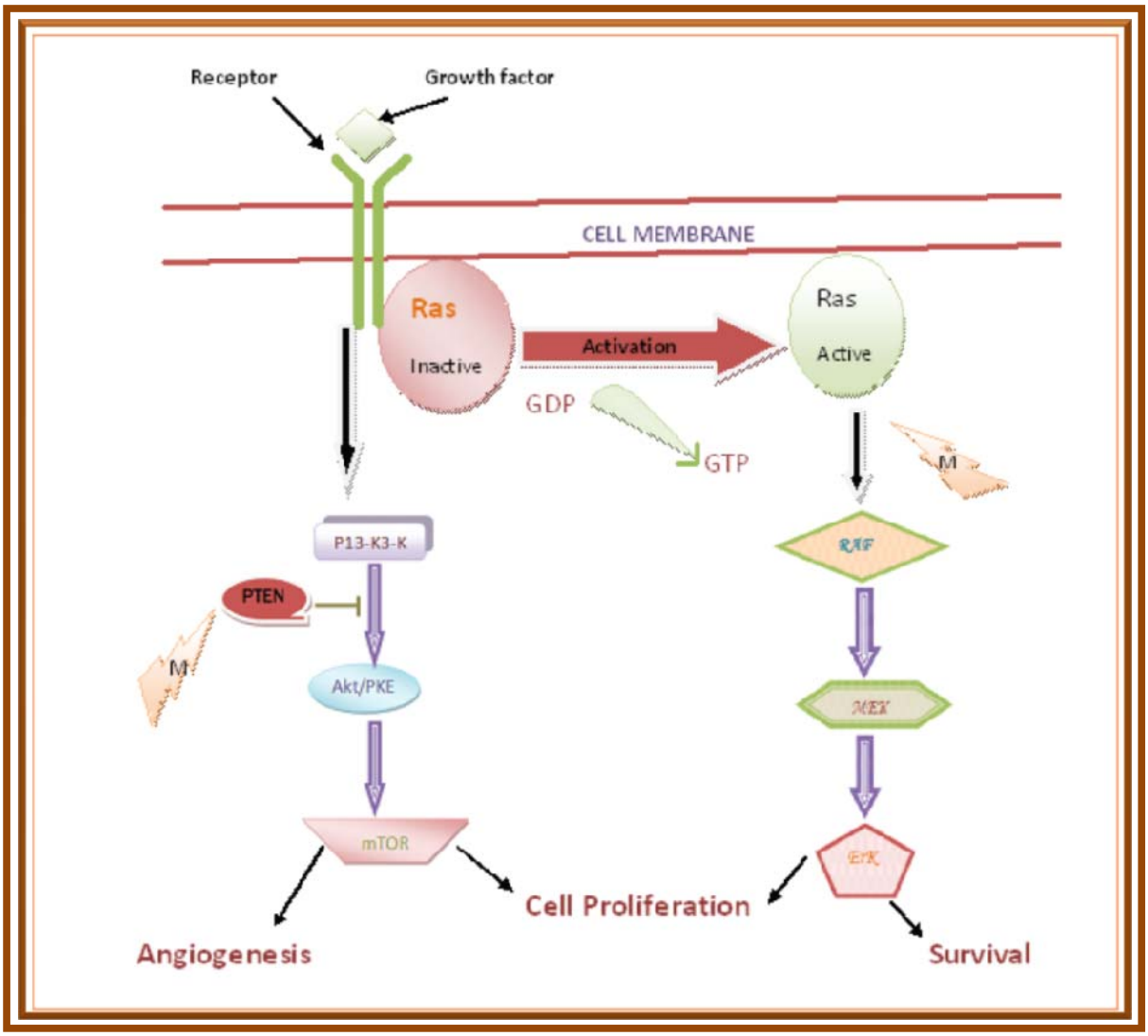

Fig. 1: Mutation in RAS/MEK/ERK and PI3K-AKT-mTOR pathway is involved in pathogenesis of BC. [MEK: MAP/ERK Kinase; ERK: Extracellular Signal Regulated Kinase; Ras: A Signal transducing molecule; P13-K: phosphatidylinositol 3 kinase; PTEN: (phosphatase/tensin: A tumor suppressor gene); M: Mutation]

PHARMACOGENOMICS

Pharmaogenomics deals with genetic differences of persons, which affect the therapeutic action and concentration in each individual (Miller and McLeod, 2007) with the aim of choosing best drug regimen for each patient on individual basis (Watters and McLeod, 2003) and to circumvent the patient by toxic effect of drug (Miller and McLeod, 2007). Pharmacogenomics plays a significant role in chemotherapy as cancer treatment is associated with severe toxicity and changeable therapeutic effect.

Pharmacogenomics verses pharmacogenetics

Pharmacogenetic and pharmacogenomic are related to cause of variation of drug effect by individual patient on genetic base. Pharmacogenetics involves the determination of change in particular gene which is thought to cause changing in effects of therapy.

Pharmacogenomic relate to all genes of person while pharmacogenetic involves the study of versatility of sequence of responsible gene to be involved in unexpected drug effect. It involves the identification of responsible gene, producing versatility in drug's reaction, in individual patient and identification of gene susceptible to disease and producing new drug targets, are also possible (Mancinelli *et al.,* 2000; Eichelbaum *et al.,* 2006).

Application of pharmacogenomics

Application of pharmacogenomics will lead to individualization of therapy, which is totally contrast to nowadays clinical practice, in which drug's effects are

studied on large group of patient regardless of their genetic based difference. In pharmacogenomics, way of research is to study the effect of drug on small population of patient. Novel technologies, satisfaction of ambiguous questions supported by law and ethics, high grade education of health care professionals and public awareness of this disease management process is very necessary for the application of pharmacogenomics (Mancinelli *et al.,* 2000). Pharmacogenomic approaches are used to evaluate the gene responsible for personalized drug effects and gene's prediction to adverse effects of a drug, developing a linkage between the drug effects and clinically important genes (Daly, 2010). Pharmacogenomics is used to enhance the desired response and decrease the peril of adverse reactions of drugs, by having personalized genetic information. Striking application of pharmacogenomics involve the enhancement of safe use of drug and modulation of disease biomarker to understand the mechanism of drug effect. Many current medications are related to problem of unexpected therapeutic and toxic effects. In identification of inherited DNA variation, pharmacogenomics is used as a tool for individualization of medication. Major causes of variability in therapeutic and toxic effect of medicine are variation in the sole nucleotide of gene encoding for enzymes, responsible for biotransformation of drug, carrier of drug, and genes involved in repairing of DNA (Thomas *et al.,* 2004).

Pharmacogenomics can predict side effects

Pharmacogenomics can evolve the deleterious reactions of drugs (Beitelshees and McLeod, 2006). Genetic variation of drug's receptor is also a cause of versatility in therapeutic effect of drug. Adverse effect of drug shown by different individual is leading cause of mortality. By the knowledge of pharmacogenetic and pharmacogenomics, this leading cause of death can be reduced (Vesell, 200). Adverse drug reaction that cannot be prevented can be control by applying pharmacogenomics, involving individualization of medication (Phillips *et al.,* 2001). Most of adverse effects of drug are thought to have involvement of many genes alongwith environmental factors. Pharmacogenomic, related to personalize drug effect can be used to reduce adverse effects of drugs. Genetic variability influences pharmacokinetic of drug which has some relation to adverse effect development (Severino and Del Zompo, 2004).

Tools of pharmacogenomics

Versatility to drug effects in a population depends upon a lot of determinants; most important of them is genetic factor. By clinical observation and use of tools, the genetic involvement in drug effects can be predicted. Clinical studies have limitation, due to problem in the use of *in vivo* system to check the natural changes and lack of ability to control the environment-related determinants. A very new tool to check the genetic involvement in versatility of drug effects is use of cell lines panels, most recent of them are International HapMap sources of widely provided data of genotype expression and phenotype. These International HapMap sources enabling the researchers to develop their own facts according to drug whose effects are suspected to have genetic involvement. Provision of human lymphoblastic cell lines from many population of world enables the researchers to determine the difference to drug effect between persons as well as between populations (Welsh *et al.,* 2009).

International HapMap samples are used as means for 1000 genome project, for provision of information about genetic polymorphism for 1000 genomes, belonging to the different population. HapMap sample is also used for discovery and validation of phrmacogenomics. The examples is, use of HapMap sample to determine the pharmacogenomics of cell killing by drugs, to evaluate genetic markers. 1000 genomes project will enables detailed study of pharmacogenomics which will lead to an increased ability to evaluate the genetic polymorphism in drug effect (Zhang and Dolan, 2010).

APPLICATION OF PHARMACOGENOMICS IN TREATMENT OF BREAST CANCER

Gene expression profiling, a technique to determine the appearance of numerous genes in tissue samples concurrently, is an emerging pinpointing means for BC. The collection of several genes will be more foretelling of prognosis than any single gene alone. Gene expression signatures have revealed forecast clinical outcome of BC plus response to meticulous chemotherapy protocol (Rouzier *et al.,* 2005).

The breast carcinomas demonstrate numerous irregularities in phosphatidylinositol 3 kinase pathways, such as PTEN failure which can be put in perspective of treatment by means of rapamycin analogues. PTEN failure in BC can take place by mutation or decline of PTEN appearance in approximately half of infrequent breast tumors. This pace of mutations is an important concern for narrative drugs in which natural effectiveness is prejudiced by the action of PTEN (Nassiri *et al.,* 2009). Highly developed benign or invasive BC is classically treated with chemotherapy. Chemotherapy protocols include anthracyclines, taxanes, antimetabolites, alkylating agents, platinum drugs and vinca alkaloids (Marsh and Liu, 2009).

Versatility in the pharmacological processes of drug between individuals and races is due to inherited variation shown by enzymes responsible for biotransformation of drug, drug binding protein (Tan *et al.,* 2008) and excretion of drug, thus affecting the effectiveness of therapy (Kiyotani *et al.,* 2010).

Active cancer (AC) therapy of BC includes doxorubicin and cyclophosphamide. ATP-binding cassette subfamily B, member 2(ABCB2) and SLC22A116 (organic cationic

transporter family) transporter use doxorubicin as a substrate. Cyclophosphamide undergoes oxidation by Cytochrome P450 2B6, Cytochrome P450 2C9, Cytochrome P450 12C19 and Cytochrome P450 3A5. Inherited variation in gene encoding for the enzymes affect the efficacy of AC therapy (Bray *et al.,* 2010).

PXR*1B is linked with decreased hepatic mRNA expression of pregnane X receptor (PXR) and Cytochrome P450 3A4 and ATP-binding cassette subfamily B, member 1 (ABCB1), targets of PXR. Patient having PXR*1B show decreased clearance of doxorubicin, suggests that PXR haplotype has an impact on versatility in the deposition of drug, between individuals and races (Brauch, 2007).

The effectiveness and development of deleterious effect of chemotherapeutic agents, in cancer patients, are dependent on the inherited polymorphism of enzymes responsible for biotransformation of drug and signaling pathways (Snozek *et al.,* 2009). The role of inherited polymorphism in the Tamoxifen (TAM) effect is a best example which exhibits the significance of pharmacogenomics (Weinshilboum, 2008).

The knowledge about the mechanism by which variation in gene of enzyme, responsible for biotransformation, carriers and binding site influence the effectiveness and unwanted effect of drug alongwith advances in genocopying methods will help the implementation of pharmacogenomic approaches in clinical setup to treat BC (Blackhall *et al.,* 2006).

Polymorphic enzymes responsible for the biotransformation of Tamoxifen

Tamoxifen (TAM), an estrogen's inhibitor is used to treat BC. TAM belongs to group of drugs which require its metabolism to perform its action by an enzyme (Barrière *et al.,* 2010). Beneficial effect of TAM depends upon various determinants; the most significant of them are polymorphic alleles for Cytochrome P450 2D6, which are involved in drug's biotransformation, effectiveness and safety of the drug (Briest and Stearns, 2009).

Metabolites of TAM are 'hydroxy TAM' and 'endoxifen' which are more active than TAM. Biotransformation of TAM to endoxifen takes place via hydroxylation by Cytochrome P450 2D6 and via demethylation by Cytochrome P450 3A (Stearns *et al.,* 2003).

Determination of sequence of Cytochrome P450 2D6 encoding gene can forecast the personalized drug effect and biotransforming ability of patient (Brauch *et al.,* 2009). 80 polymorphs of the gene of Cytochrome P450 2D6 have been discovered. The four phenotypes of Cytochrome P450 2D6 are: very fast metabolizers, fast metabolizers (FM), intermediary metabolizers and slow metabolizer (Barrière *et al.,* 2010). The metabolizing power of Cytochrome P450 2D6 is calculated by inherited variation and enzyme inhibition, a forecaster for result of BC in elder females, on hormonal therapy (Goetz *et al.,* 2007).

About 5-8% of Caucasian patients are Cytochrome P450 2D6 "insufficient metabolizers" on an inherited base and is comparatively incapable to catalyze TAM metabolism (Weinshilboum, 2008).

In premenopausal BC patient having reduced and intermediary drug metabolism level, the effective therapy is to increase the dosage of TAM or use of LH-RH (luteinizing hormone-releasing hormone) analogue or co-administration of aromatase inhibitors (AI). In postmenopausal females, having fast metabolism, the effectiveness of TAM is same as of AI (Barrière *et al.,* 2010).

UDP-glucuronosultransferases is a group of enzyme responsible for clearance of TAM and its metabolic product. This enzyme also has an impact in variation of drug's effect between different individuals (Lazarus *et al.,* 2009).

Efficacy of Tamoxifen depends upon Cytochrome P 450 2D6 Polymorphism

Genetic variation for Cytochrome P450 2D6 is resulted with changed endoxifen concentration in plasma (Jin *et al.,* 2005). Patient's inheritance, mainly the existence of 2 worthless alleles, can be used to forecast about the therapy of BC, prevention, recurrence of disease and possible prognosis. An application of pharmocogenomics has shown that variation in the only one nucleotide in gene, encoding Cytochrome P450 2D6, decreases TAM effectiveness (Higgins *et al.,* 2009).

BC patient with inherited variation in Cytochrome P450 2D6, exhibit inferior plasma concentration of endoxifen, thus reducing the efficacy of TAM. Cytochrome P450 2D6 is forecaster of rumination of TAM, on personalized basis (Stearns and Rae, 2008).

Determination of Genetic sequence of Cytochrome P450 2D6 and the use of Cytochrome P450 2D6 inhibitors are related with plasma concentration of endoxifen and have an impact on TAM treatment (Borges *et al.,* 2006). The effectiveness of the TAM is increased in the patient having Cytochrome P450 2D6*2A allele. Concomitant use of Selective Serotonin Reuptake Inhibitors (SSRI), Cytochrome P450 2D6 inhibitors, and TAM causes the change in TAM action (Jin *et al.,* 2005). Agents which can inhibit the activity of Cytochrome P450 2D6 should not be taken by BC patient, on hormonal therapy (Goetz *et al.,* 2007).

Selective serotonin reuptake inhibitors are responsible for inferior biotransformation of TAM as well as

effectiveness of drug (Stearns *et al.,* 2003). The aromatase inhibitors represent a major class of drugs in the treatment of BC. Inherited difference in the Cytochrome P450 19 gene (aromatase gene) may be central in the action of aromatase inhibitors. The aromatase gene has shown considerable decreases in levels of activity of aromatase inhibitors (Ingle, 2008). Aromatase inhibitors have an increased effect to reduce the relapsing than the TAM, in BC patients having estrogen receptor (Punglia *et al.,* 2008).

Patient having the reduced metabolizing ability of TAM has lower concentration of endoxifen thus reduced effect of TAM than patient having increased metabolizing ability of TAM (Beverage *et al.,* 2007).

Is genotyping of Cytochrome P450 2D6 prior to treatment is beneficial?

Estimation by genetic information, before the hormonal treatment, is well thought out for females who have recently detected with BC (Punglia *et al.,* 2008). The proceeding knowledge of pharmacogenetic variants which cause inhibition of Cytochrome P450 2D6 enzyme, responsible for biotransformation of TAM, can provide contrivance for personalization of endocrine treatment of BC (Goetz *et al.,* 2008). The choice of therapy in BC depends upon some forecasting markers (Hertz *et al.,* 2009). Reliable expression profile has demonstrated the role of some other genes in effectiveness of therapy for BC, in addition to common predictive markers. So there is a need of some set of forecasting experiments, used to determine the marker, to forecast the effectiveness of therapy (Rody *et al.,* 2006). Genotyping of Cytochrome P450 2D6 may act as pharmacogenetic implementation, for making the hormonal therapy of BC more beneficial (Hoskins *et al.,* 2009). For BC, Cytochrome P450 2D6 condition has been taken as an autonomous forecaster for the result of TAM. Thus, a more optimized TAM treatment is possible through a former inherited evaluation of Cytochrome P450 2D6 (Kirchheiner, 2008). Invasive BC are treated with endocrine therapy i.e. TAM. If the action of Cytochrome P450 2D6 is disturbed due to genetic variation or drug interaction, it will lead to increased relapsing of disease. Phrmacogenetic testing is available for forecasting of effect of TAM by Cytochrome P450 2D6 genocopying (Gaston and Kolesar, 2008). The unwanted effect of TAM is hot flashes. There is a relation between Cytochrome P450 2D6 status and frequency and severity of hot flashes. Less rigorous hot flashes are shown by patient having reduced rate of biotransformation compared to intermediary and increased biotransformation level. So genocopying of Cytochrome P450 2D6 may be a forecasting determinant for TAM induced hot flashes (Lynn Henry *et al.,* 2009). Genocopying of Cytochrome P450 2D6 does not relate with toxic effects of TAM therapy, either brutal, serene, or no toxicity (Ramóny *et al.,* 2010). Progesteron receptor status in BC patient lacking estrogen receptor (ER) give information that TAM may prove beneficial for such patient, but these patients are different who are assessed on estrogen receptor status alone (Dowsett *et al.,* 2006). Genocopying of Cytochrome P450 2D6 allele of *4,*5,*10,*41 can predict the result of TAM treatment. Cytochrome P450 2C19*17 polymorph give information that TAM treatment is how much beneficial for that particular patient (Brauch, 2007).

Cytochrome P450 2D6 genocopying prior to therapy to forecast metabolizer's position may open new horizon for personalization of hormonal therapy with the greatest advantage being estimated for fast metabolizers. Furthermore, Cytochrome P450 2D6 inhibitors like SSRI, given to treat hot flashes, must not be used as they brutally weaken the formulation of biotransformation products (Brauch *et al.,* 2009). TAM disturbs the lipid level in body. It decreases low density lipoprotein and increase triglycerides. Variation in the gene Cytochrome P450 2D6 gene, estrogen receptor-1 (α) gene (ESR1), estrogen receptor-2 (ß) gene (ESR2), is thought to have an effect on this deleterious effect of TAM. In postmenopausal females, change in low density lipoproteins level caused by TAM is linked with polymorphic gene ESR1-Xbal, while changes of triglycerides are linked with ESR2-02. In premenopausal females polymorphic gene ESR1-Xbal is linked with changes in triglycerides, by TAM. So genocopying of estrogen receptor can be proved as a forecaster about response of patient on TAM therapy (Ntukidem *et al.,* 2008).

Prognosis of breast cancer linked with gene ploymorphism

Prognosis of BC is linked with Cytochrome P450 2D6 polymorphism. Patient with 2 serviceable Cytochrome P450 2D6 allele show good prognosis and those with variant functionless Cytochrome P450 2D6 allele show inferior prognosis (Schroth *et al.,* 2009). For anthracyclines, variation in genes e.g., carbonyl reductase 3 (CBR3), ATP-binding cassette subfamily B, member 1 (ABCB1), glutathione-related transporter genes, and oxidative stress-related genes are related with prognosis of disease (Tan *et al.,* 2008). Variation in Cytochrome P 450 2D6 and ATP-binding cassette subfamily B, member 2 (ABCC2) are chief forecaster for the prospects of patients with BC treated with TAM (Kiyotani *et al.,* 2010). Variation in only one nucleotide in ABCB1 has an impact on functionality of P- glycoprotein, estrogen receptor (ER) and clinical outcomes (Vaclavikova *et al.,* 2008). Post menopausal females having non-aberrant variation in Cytochrome P 450 2D6, show bad prognosis as compared to females carries wild type genotypes (Hartman and Helft, 2007). The patients having ABABI 2677A, Cytochrome P 450 2B68, Cytochrome P 450 2B69, Cytochrome P 450 2B64 alleles show bad prognosis (Bray *et al.,* 2010).

Resistance to therapy leads to relapsing

Resistance to TAM by some patients is due to single polymorphism in gene encoding for Cytochrome P450 2D6. The genetic polymorphism in Cytochrome P450 3A4 can also envisage the effect of TAM treatment, carriers of *3 allele are on augmented hazard of relapsing of disease (Wegman *et al.,* 2007). Among the patients of BC treated with TAM, females having Cytochrome P450 2D6 *4/*4 allele lead to an increase danger of recurrence and lower occurrence of hot flashes (Goetz *et al.,* 2005).

Modification in appearance of key genes through abnormal epigenetic directive in breast cells can lead to instigation, endorsement and continuation of carcinogenesis, and is even concerned in the production of resistance to therapy. Epigenetic directive has been known to involve three mutually interacting events: DNA methylation, histone modifications and nucleosomal remodeling (Lo and Sukumar, 2008).

Tumors having Human Epidermal growth Factor Receptor 2 (HER2) show resistance to TAM (Dowsett *et al.,* 2006). TAM resistance can be identified by HER and progesterone receptor status. Aromatase inhibitors have an increase effect to the patient with absent progesterone receptors (Tovey *et al.,* 2005).

BC patients having Cytochrome P450 2D6*10 allele, responsible for decreased Cytochrome P450 2D6 activity, are on an elevated peril of relapsing than those patients which are homozygous for wild type Cytochrome P450 2D6*1 allele. Genetic sequence of Cytochrome P450 2D6 has an influence on relapsing of disease. Patient having the genetic sequence of Cytochrome P450 2D6*10/*10 have small period between relapsing than those with Cytochrome P450 2D6 *1/*1 with other aspects accustomed (Kiyotani *et al.,* 2008). There is considerable inter- person variation in the improvement of resistance to TAM therapy, and in the occurrence of TAM-induced adverse events, including deep vein thrombosis, hot flashes, and the development of endometrial cancer (Goetz *et al.,* 2007).

CONCLUSION

To get the best results from treatment of breast cancer by Tamoxifen, pharmaogenomic approach has its own importance. The genetic differences in persons, affect the therapeutic action and concentration of Tamoxifen in each individual. Therefore it is concluded to choose best drug regimen for each patient on individual basis and to circumvent the patient by toxic effect of drug.

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