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Review Article

Hormonal Therapy in Breast Cancer: Consideration of Pharmacogenetics

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Abstract: Hormonal imbalance in postmenopausal women makes them susceptible to various menopausal symptoms and hormonal replacement therapy (HRT) is the treatment option for them. However, various concerns are involved with this therapy due to increased risk of pulmonary embolism, stroke, coronary heart disease, and even cancer. Especially long term use of single or multiple hormones at the same time appears to be more associated with unwanted disorders. However, few of the reports say that hormonal therapy with estrogens protect women against breast cancer. While there exist wide range of studies to address this issue, genetic profile of the patient are also important prior to HRT. Certain gene profile women are more or less susceptible to cancer risk. In this review we will discuss about various genetic factors related to this issue.

Keywords: Hormonal imbalance, postmenopausal women, hormonal replacement therapy (HRT).

INTRODUCTION

Menopausal symptoms as well as chronic diseases such as osteoporosis and cardio vascular disease can be treated managed with the HRT [1]. Despite the health benefits, HRT also is a risk factor for serious diseases including, breast, ovarian and endometrial cancer. However, the exact role of HRT in cancer and further the reports were not consistent when comparing multiple studies. Ovulation hypothesis, other hormonal levels in the body, differences in affinity of estrogen towards estrogen receptors due to pharmacokinetic and absorption profile should be considered for detailed understanding [2-4]. The risk-benefit analysis should be properly weighed in and out before starting the HRT. The levels of hormones in the body should be strictly maintained based upon the person's biological/hormonal profile [5]. Various types of formulations are already available in the market and being active studies to deliver estrogen and progesterone like compounds [6-8]. The objective of variety of formulations is to maintain drug concentrations in the blood at a specific rate and reach pharmacological benefit [9]. Hormonal formulations, anticancer drugs, and cardio vascular related drugs need to be formulated in right method for proper affect as they possess significant adverse effects if not maintained properly [10-13]. Recently, drug implants are also being developed for this purpose. These implants release the drug at a constant rate for particular period of time by staying under the skin [14]. Transdermal route of administration is more interested in recent days as skin provides huge surface area and gets one-third of total blood supply. Topical formulations meant for transdermal application of testosterone, estradiol and other hormone compounds are developed [15, 16]. Instead, oral delivery of hormones can be done in effective way by using nanoparticles for improved oral absorption and bioavailability [17, 18]. Estrogen and progesterone are the lipophilic compounds and need aid of the formulation for maximum absorption. PLGA is a biodegradable polymer and used in formulations in variety of applications. PLGA nano particles were prepared with estrogen which showed promising results by increasing intestinal uptake and effective zero order drug release [19].

Studies suggest that there is increased risk of breast cancer in postmenopausal women due to imbalance in hormonal levels in the body. High levels of estrogens in postmenopausal women is associated with increased body mass index (BMI) and further can lead to breast cancer. Body mass index is a factor used to estimate the obesity occurrence. Analysis of the eight prospective studies that were conducted in postmenopausal women indicated these interesting results about the relation between body mass index, estrogen levels and cancer in them. Adjusting the estradiol or other estrogen levels had reduced the relative risk of breast cancer or breast cancer risk [20]. In a separate meta-analysis study of 89 epidemiologic reports, complex relationship between BMI, menopausal status, breast cancer sub type and hormonal use were analyzed [21]. They also found positive

relationship between premenopausal breast cancer and obesity where BMI is greater than 30. Moreover, in case of hormonal receptor positive postmenopausal breast cancer and obesity, the risk ratio is 1.39 compared to the 1.06 of hormone receptor negative breast cancer. These studies indicate that hormonal balance in postmenopausal women is a critical factor to estimate the breast cancer risk. Hence hormonal replacement therapy should be weighed for its advantage over the breast cancer occurrence in the women [22].

Interest in pharmacogenomic studies is increasing in recent years. The major goal of this area to understand and explore the inherited nature of drugs or other treatment compounds in body in terms of their metabolisms, excretion, pharmacological affect, and toxicity. This analysis helps us in drug discovery process along with its optimization according to the patient profile. Any differences in between individuals can be tracked to adjust the therapy. However, this field requires some technology to help diagnosing and identifying the genetic differences in respect to the treatment for best personalized treatment. After administration, drug has to pass through several phases such as metabolism, elimination, and interaction with target. Any genetic differences in these genes which can affect their function will affect the drug treatment outcome leading to inter individual variations [23]. Single nucleotide polymorphisms (SNPs) are observed either in promoter or coding region of the gene. This alteration results in altered function or expression of the enzyme/protein associated with drug fate in the body. Differences between wild type and mutated proteins are cause for altered drug functions.

Hormone replacement therapy and genomic differences

Combined hormonal replacement therapy (CHRT) is used in postmenopausal women to treat menopausal symptoms [24]. CHRT includes the administration of estrogens and progestins. However, CHRT can result in or increase the breast cancer risk in some women with certain genotypes. It does not cause breast cancer in all the treatment women but only the susceptible women expressing a specific genetic variants or gene polymorphisms in hormone metabolizing enzymes are at increased risk. Cytochrome P450 group of enzymes are in liver are responsible for metabolism of hormones. In addition, progesterone receptor (PGR) also plays a role in progestin regulation. In a population based study, postmenopausal women were studied for their metabolism genotype differences at CYP3A4 and the progesterone receptor (PGR) to observe effects on breast cancer risk [25]. The human progesterone receptor (hPR) has two isoforms known as hPR-A and hPR-B. Whereas they are encoded by a single gene, PGR [26]. Variant of the gene, 331A allele, results in excessive transcription of hPR-B isoform compared to the hPR-A. The hPR-B isoform is associated with transcriptional activation [27] and carriage of the 331A allele in women promotes breast cell proliferation at higher rate. Accordingly, women consisting of PGR 331A allele of progestin receptor, are susceptible to ductal carcinoma risk if they are undergoing CHRT treatment for 3 or more years. Moreover, these women are prone to progesterone positive tumors with odds ratio of 3.82. In case of women without CHRT and CYP3A4*1B allele, there exists an increased risk of estrogen receptor negative tumors [25]. CYP3A4 is responsible for metabolism of progestins and estrogens to their respective hydroxylation forms. CYP3A4*1B is an A/G nucleotide change at position-290. CYP3A4*1B alleles are found in Caucasians more frequently. CYP3A4*1B is correlated with higher expression of the enzyme [28] and further causes increased metabolism of progestins and further decreases the breast cancer risk in postmenopausal women receiving CHRT [29]. At the same time, progestins metabolism is very less in CYP3A4*1A patients compared with CYP3A4*1B variants. If correlation between Cyp3A4 and PGR is assessed, we can identify the women susceptible to breast cancer and take precautions while giving the CHRT. These susceptible women need increased breast surveillance or be good candidates for other preventive strategies.

Anti-estrogen treatment: Gene polymorphisms

Breast cancer is a major problem in women around the world. The mutations of the cancer make it more difficult to treat [30, 31]. It can be characterized based upon the high expression levels of estrogen receptor (ER) or progesterone receptor (PR). Based on these receptor levels, hormonal chemotherapy is suggested in patients. Most of the breast cancers show presence of estrogen receptors on their surface and are called estrogen dependent (ER positive cancers). Anti-estrogen therapy like administration of Tamoxifen and aromatase inhibitors are treatment options in this case [32]. Tamoxifen is very much used is breast cancer treatment and tamoxifen-metabolizing enzymes are highly polymorphic. Genetic polymorphisms in the enzymes are associated with inter individual or interethnic differences in Tamoxifen treatment efficacy and prognosis. CYP3A4*1B alters tamoxifen metabolism, and can increase risk of endometrial cancer in tamoxifen treated women [33, 34]. In a study on postmenopausal women treated with tamoxifen, who were homozygous for the CYP3A5⁄3C variant, displayed significantly improved recurrence-free survival [35]. CYP2C19 gene is associated with survival rate in breast cancer patients receiving Tamoxifen treatment. CYP2C19 wild type patients have less survival rate whereas CYP2C19 681AA variants have longer survival rate. CYP2C19 681G>A, and 636G>A variants have lack of enzyme activity, and are associated with an increased breast cancer mortality rate [36]. The SNPs in CYP2D6 depend upon the race and ethnicity [37, 38]. In a study on 618 breast cancer

patients treated with adjuvant tamoxifen, CYP2D6*4, *5, *10 and *41 alleles were genotyped and the recurrence free survival (RFS) was calculated. If the CYP2D6 alleles with low or reduced enzymatic action are expressed in patients, there exists a non-significant trend for RFS [39]. In another study, when compared with the functional alleles, the patients carrying the nonfunctional alleles of CYP2D6 gene had significantly more recurrences of breast cancer, shorter relapse-free periods, and worse event-free survival [40]. But if the patients are taking CYP2D6 inhibitors during Tamoxifen therapy, the clinical outcome will be altered. But usefulness of CYP2D6 genotype testing to assess the advantages and disadvantages of Tamoxifen therapy is still not clear. Third generation aromatase inhibitors can be used in place of Tamoxifen therapy in postmenopausal women with hormonal positive breast cancer [41]. Other than CYP2D6 metabolizing enzyme, SULT1A1 and UGT enzymes also play an important role in metabolizing the Tamoxifen. The SULT1A1⁄2 variant (638G>A, Arg213His) results in protein with reduced enzymatic activity. So Tamoxifen is not fully metabolized and this condition is associated with increased death rate in Tamoxifen treated patients [42]. In tamoxifen-treated breast cancer patients, patients with SULT1A1 *2/*2 and either UGT2B15 *1/*2 or UGT2B15 *2/*2 had a significantly reduced 5-year survival [43].

Estrogen receptor (ER) pharmacogenetics

ER was shown to consist of Asp351Tyr and Tyr537Asn point mutations that are associated with altered response to estradiol and antiestrogens [44, 45]. Few polymorphic forms of ERα and ERß genes have been related to higher breast cancer risk [46]. Two common variants of ERα are PvuII (rs2234693) and XbaI (rs9340799) polymorphisms. These forms are present upstream of exon 2 of the ERα gene. A study on 1069 patients showed that the PvuII and the (GT)n polymorphisms of ERα gene are strong prognostic indicators of survival in women with ER positive breast cancers [47].

CONCLUSION

Hormonal therapy is the widely accepted and suggested treatment for postmenopausal symptoms in women. However, some of the treatment benefits are outweighed by the potential health risks including cardiovascular or breast cancer problems. Hence before initializing the therapy, clinical factors and genomic profile of the person should be considered to individualize the therapy. Health life style and food habits needed to be encouraged by the postmenopausal women.

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