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Title : INTERPATIENT VARIABILITY IN TAMOXIFEN RESPONE AMONG BREAST CANCER PATIENT: THE USE OF PHARMACOGENETICS AND METABOLOMICS IN CLOSING THE GAPS IN CLINICAL PRACTICE

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Tamoxifen has been widely used as the standard adjuvant therapy for breast cancer patients with oestrogen receptor-positive status, especially in the high-risk pre- and postmenopausal women. However, 30 to 50% of ER-positive breast cancer patients do not respond to tamoxifen therapy. Major challenges to effective tamoxifen therapy include drug resistance, and adverse events. Thus, this study aims to investigate the impact of pharmacogenomics and metabolomics in monitoring the efficacy of tamoxifen treatment in BRCA patients. A total of 95 tamoxifen-treated patients, and 11 untreated breast cancer patients from three major Malaysian ethnic groups (Malay, Chinese and Indian) were recruited. However, only 84 tamoxifen-treated patients with completed clinical data were included for clinical association analysis. Blood and plasma samples were collected to obtain DNA, RNA, and metabolites, and clinical data of the patients were also collected. Investigations proceed with the genotyping of *CYP2D6* and *ABCB1* using multiplex allele specific PCR (ASPCR) approach. Patients carrying *CYP2D6 *10/*10* and heterozygous null allele (IM) showed higher risks of developing recurrence and metastasis (OR, 13.14; 95% CI, 1.57 – 109.94; P = 0.004) compared to patients with *CYP2D6*1/*1* and **1/*10* genotypes. Patients with homozygous *CC* genotypes of *C3435T* had shown to have shorter recurrence time. Patients who were *CYP2D6* IM and homozygous *CC* genotype of *C3435T* had statistically significant higher risks of recurrence (P = 0.002). Similarly, median time to recurrence in these patients was only 12 months (95%CI = 0.79 - 23.2) compared to those without this combination, which was 48 months (95%CI = 14.7 - 81.2). Patients with *CYP2D6 IM* and homozygous *CC* genotype of *ABCB1 C3435T* have shorter times to recurrence. The expression of oestrogen receptor-α and oestrogen receptor-β from the samples were quantitated using Real-time PCR. Absolute quantification of ERs reveals that the over-expression of *ER-α* in peripheral blood has positive correlation with the expression of *ER-α* in breast cancer tissue. The developed method would be useful as it is less invasive, and can be used to monitor a patient's progress towards disease and drug therapy. Furthermore, the patients were also subjected to denaturing high performance liquid chromatography (dHPLC) analysis to navigate the entire exon region of *ER-α*. There were a total of 3 variants sites detected and further analysis on *ER-α* SNPs revealed that *CC* genotype of *C325G* causes an increased risk of recurrence (P = 0.027). Global metabolic profiling was performed by Quadrupole Time-of-Flight (Q-TOF) in conjunction with multivariate data analysis and pathway analysis. A total of eight groups of compound were detected to have potentials to be developed into biomarkers. Pathway analysis showed that steroid hormone biosynthesis, aminoacyl-tRNA biosynthesis, tryptophan metabolism, fatty acid metabolism, and sphingolipid metabolism were affected in BRCA patients. This pilot study demonstrates that the integration of pharmacogenomics and metabolomics into conventional therapeutic drug monitoring could enhance the characterization of prognosis as well as the patients' response towards therapy. This would allow more personalized treatment to patients, thus allowing better chances of success in individual therapy.