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Title of the Thesis: Study on *CYP2D6* and *ABCB* polymorphisms with respect to Tamoxifen adjuvant treatment in ER and PR breast cancer patients

Submitted by: Smt. Tanuma Mistry

ABSTRACT

Breast cancer (BC) is a highly heterogeneous malignancy with the highest global prevalence. Effective management necessitates a multimodal therapeutic approach to mitigate disease severity and enhance survival outcomes. Among chemotherapeutic regimens, anthracycline-taxane based therapy remains a cornerstone of treatment. However, its clinical utility is often constrained by substantial toxicity, primarily attributed to inter-individual variability in drug transport and metabolic pathways, underscoring the need for personalized therapeutic strategies. This study aims to elucidate the pharmacogenetic influence of *ABC* and *CYP* gene polymorphisms on treatment outcomes in BC patients, with a particular emphasis on the impact of Body Mass Index (BMI). Moreover, the study seeks to determine correlations between genetic polymorphisms and therapeutic efficacy, toxicity, quality of life (QoL), and overall survival (OS) which might contribute to the development of personalized treatment strategies, optimizing therapeutic benefits while minimizing adverse effects. The study was conducted with 148 newly diagnosed non-metastatic BC patients who received (FEC/TAC/AC-T) chemotherapy followed by surgery or surgery followed by chemo ± adjuvant radiation-therapy. Expression of ER, PR, and HER2/neu was assessed by IHC. The peripheral venous blood was collected and the genomic DNA was isolated by the phenol-chloroform method. Genetic polymorphisms of *ABC* and *CYP* gene were evaluated by PCR-RFLP method. Combine effect of gene polymorphism and BMI were assessed. QoL was recorded by utilizing FACT-B and FACIT-Sp-12 questionnaire at baseline, 3rd, 6th and 12th month. Toxicity was evaluated according to CTCAE v.1. Survival outcome were noted after 48 months. Recruited patients was categorized: complete (CR 38.51%), partial (PR 12.16%), non-responders (NR 49.33%). Few patients faced chemo-induced high grade toxicities: anaemia (1.6%), diarrhoea (1.6%), constipation (1.6%), etc. Moreover ER positive tumors were associated with poor response amongst low BMI group ($p<0.05$). A significant association was found between PFS in NACT and DFS in NRs group ($p<0.0001$). The TAC regimen (HR 1.585) and AC-T regimen (HR 1.077) showed increased hazard risk for survival ($p>0.05$). A significant correlations observed between BMI groups in functional, social, and emotional QoL aspects ($p<0.05$), with no notable differences in other domains, indicate poor QoL in low BMI group compare to normal and obese patients. A significant link observed between BMI and treatment response ($p<0.0001$), showing higher rates of NRs among underweight patients ($p=4.259e^{-14}$). Homozygous recessive genotypes (AA in *ABCC2* gene and AA in *CYP2C19*) carrying patients bearing low BMI level was involved in poor chemotherapy response across all genetic models ($p<0.05$) and also involved in poor survival ($p<0.05$) and increased hazard risk in low BMI patients (HR>1). Our findings indicate that polymorphisms in metabolizer (*CYP2C19*: AA) and transporter (*ABCC2*: AA) genes, in conjunction with low BMI, were associated with poor treatment response and worst survival outcomes in BC patients. Furthermore, patients with low BMI exhibited significantly lower QoL scores compared to those with normal or obese BMI. Among anthracycline-taxane regimens, the AC-T demonstrated superior clinical efficacy and survival benefits. Collectively, this study highlights the necessity of pre-treatment dietary consultations as a standard of care for Indian BC patients, alongside the integration of genetic counseling and nutritional support to optimize therapeutic outcomes.

Tanuma Mistry.
Full Signature of the Candidate

Forwarded & Recommended,

Vasare
Signature with Seal of the Supervisor

Vilas D. Nasare, Ph.D.
Senior Scientific Officer
Pathology & Cancer Screening
Chittaranjan National Cancer Institute
37, S.P. Mukherjee Road,
Kolkata - 700 026, INDIA