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POSTER SESSION

Pharmacogenetics

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Optimizing adjuvant endocrine therapy for postmenopausal breast cancer: the modified CYP2D6 genotype-based modeling analyses

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Purpose: A previous modeling analysis suggests that postmenopausal breast cancer women with wild-type CYP2D6 (non-CYP2D6*4-allele carriers) might actually have superior disease-free survival (DFS) outcomes when they take tamoxifen rather than an aromatase inhibitor (AI). The present study not only adjusts that original model by the comedication status of CYP2D6-inhibitors but also reconstructs a multiple-genotype-based model, so that an optimizing endocrine therapy for patients harboring wild-type CYP2D6 would be exactly determined.

Methods: We created Markov models (a modified model and a reconstructed model) to determine whether tamoxifen or AIs maximized 5-year DFS for extensive-metabolizer patients. We also employed two-way sensitivity analyses to explore the impacts of hazard ratio (HR) of decreased metabolizers and frequency of each metabolizer on DFS by studying a range of estimates.

Results: In the comedication-adjusted model, the 5-year-DFS of tamoxifen-treated extensive-metabolizer patients was 84.7%, similar to or slightly superior to that for genotypically unselected patients receiving AIs (84.0%). Similarly, in the reconstructed model, the extensive-metabolizer patients also benefited more from tamoxifen than from AIs (5-year-DFS, 85.7% vs. 84.0%). Our reconstructed model with two parameters simplified the prediction of tamoxifen response and increased the reliability. Two-way sensitivity analyses demonstrated the robustness of these results.

Conclusions: Our modeling analyses indicate that among extensive-metabolizer patients, DFS outcomes of patients receiving tamoxifen are similar to even superior to those receiving AIs. The findings strongly suggest that postmenopausal patients who are concerned about the toxicity or cost of AIs could refer to the CYP2D6 genetic testing to pursue an optimal adjuvant endocrine treatment.

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CYP2D6 genotype and optimization of breast cancer treatment

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Background: Tamoxifen continues to be a standard endocrine therapy for the prevention and treatment of estrogen receptor (ER)-positive breast cancer. Tamoxifen can be considered a classic "pro-drug",' requiring metabolic activation to elicit pharmacological activity. CYP2D6 is the rate-limiting enzyme catalyzing the conversion of tamoxifen into metabolites with significantly greater affinity for the ER and greater ability to inhibit cell proliferation. The CYP2D6 gene is highly polymorphic, currently with more than sixty different major alleles known, many of which are associated with increased, decreased, or abolished function of the final gene product. The CYP2D6 phenotypes associated with these different alleles include poor (PM), intermediate (IM), extensive (EM), and ultrarapid (UM) metabolizers. The main purpose of this work is to study genotypes and phenotypes of CYP2D6 as well as plasma concentrations of tamoxifeno and its major metabolites (N-desmethyl-tamoxifen, 4-hydroxy-tamoxifen and N-desmethyl-4-hydroxy-tamoxifen) in women with breast cancer treated with tamoxifen.

Material and Methods: Sixty women with breast cancer who were in treatment with 20 mg/d of tamoxifen in a period lesser than five years, were included in the study. Genotyping was performed by AmpliChip CYP450 Test (Roche diagnostics®) which combines gold standards in PCR and microarray technology. It has allowed distinguishing 29 polymorphisms in the 2D6 gene, including gene duplication and deletion and 2 major polymorphisms in the 2C19 gene. Plasma concentrations of tamoxifen and its major metabolites were analyzed by gas chromatography GC/MS-MS.

Results: As expected, the most frequent alleles were *1, *4 and *2. CYP2D6*4 was the most common null allele and the only allele present in PM/PM genotype patients. Mean plasma concentrations of 4-hydroxytamoxifen and Ndesmethyl-4-hydroxy-tamoxifen were significatively lower than concentrations of tamoxifen and N-desmethyl-tamoxifen in every genotype.

Conclusions: Our findings suggest that both genetic and environmental (drug-induced) factors that alter CYP2D6 enzyme activity affect tamoxifen treatment outcomes. CYP2D6 may provide a means by which the hormonal therapy of breast cancer can be individualized.

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The expression of CYP1B1 predicts neutropenia after adjuvant chemotherapy in breast cancer patients

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Background: For patients with early breast cancer, adjuvant chemotherapy is one of the mainstay treatments. However, such treatment is associated with side effects including nausea, vomiting and myelosuppression (especially neutropenia). There is wide variability in the response of individuals to standard doses of chemotherapy. This is an important problem in clinical practice, as it can lead to therapeutic failures or adverse drug reaction. Some of this variability is due to genetic factors. CYP1B1 expression was previously found to be associated with sensitivity to chemotherapy-induced toxicity. To explore the relationship between CYP1B1 expression and clinical neutropaenia toxicity, we examined 29 Chinese female breast cancer patients who underwent standard doxorubicin-cyclophosphamide regimen.

Patients and Methods: This is a prospective longitudinal study. Breast cancer patients who were planned for adjuvant AC chemotherapy [consists of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1 of a 3-weekly cycle] were consented to the study. During each cycle of chemotherapy, the complete blood count of each patient were assessed prior to and on around day 10. Prior to the cycle of therapy, blood was also taken for CYP1B1 mRNA expression using real-time quantitative PCR. Chemotherapy-related toxicity was collected according to NCI CTC version 3 toxicity criteria. Patients were divided into non-toxic group if they did not experience grade IV neutropenia, one-cycle or multi-cycle toxic groups if they suffered toxicity once or more than once of grade IV neutropenia during the treatment. Mann-Whitney U tests was used for statistical analysis.

Results: 15 patients (52%) in the non-toxic group, 7 (24%) were in the one-cycle toxic group and another 7 (24%) were in the multi-cycle toxic group. Mann-Whitney U tests revealed that the CYP1B1 expression of patients in the multi-cycle group were significantly higher than the other two groups ($P = 0.024$). Linear regression revealed that CYP1B1 expression declined over the four cycles of treatment in non-toxic group, but increased at different rates in one-cycle and multi-cycle patients.

Conclusion: This result suggested that more intense CYP1B1 induction was associated more severe chemotherapy-related neutropaenia, and thus, CYP1B1 might be a good biomarker for chemotherapy-related neutropaenia in breast cancer patients.