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Adjuvant Endocrine Therapy in Younger Women With Breast Cancer − Determinants of Interruptions Vary Over Time

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Background: In premenopausal women with hormone receptor-positive breast cancer (BC), 5 years of tamoxifen is recommended to prevent recurrence and mortality. High adherence and appropriate persistence are needed to obtain an optimal clinical benefit. Although some studies have shown that younger women with BC are at higher risk of tamoxifen interruption, little is known about reasons for interruption in this population. The aim of this study was to estimate the incidence of first tamoxifen interruption and its correlates among younger women.
Materials and Methods: This study was performed in the prospective cohort ELIPPSE40, a French representative sample of women with BC stages I, II and III, aged 40 or less. The 196 women diagnosed between September 2005 and July 2008 with hormone receptor-positive BC were interviewed at enrolment and at 10, 16, and 28 months after diagnosis; their medical and prescription refill data were available.
Tamoxifen interruption was defined as two or more consecutive months without dispensed prescription of tamoxifen, as indicated by the national prescription database. On the assumption that reasons for discontinuation may vary over time we studied two periods: between tamoxifen initiation and 16 months after BC diagnosis and between 16 and 28 months after BC diagnosis.
Results: Among women treated with tamoxifen, 41% interrupted during their first 20 months of treatment. During the first period we found that treatment interruptions were mostly related to a lack of understandable information about treatment ($p = 0.01$), and insufficient social support ($p = 0.03$). During the second period another set of factors were associated with tamoxifen interruption as follows: treatment side-effects ($p = 0.01$), no longer fearing cancer relapse ($p = 0.02$), lack of social support ($p = 0.04$), no opportunity to ask questions at the time of diagnosis ($p = 0.01$) and low initial therapeutic sequence ($p = 0.04$).
Conclusions: A high rate of young women with BC interrupted tamoxifen. Improving information about the objectives and potential side effects of taking tamoxifen as well as improved patient-provider relationship might prevent interruption. Particular attention should be paid to women with little social support.

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The Combination Analysis of Cell Cycle Profiling-Risk Score, Ki-67 Expression, and Glutathione S-transferase P1 Expression Predicts Pathological Response to Neoadjuvant Paclitaxel Followed by FEC in Breast Cancers

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Background: We have demonstrated that cell cycle profiling-risk score (C2P-RS) based on CDK1 and CDK2 specific activities may reflect the growth speed and be a useful marker of not only prognosis but also prediction in breast cancers (BC). The aim of this study is to evaluate whether the combination analysis of C2P-RS with Ki-67 and glutathione S-transferase P1 (GSTP1) expressions can predict pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) more accurately than C2P-RS alone. We expected adding Ki-67 and GSTP1 expressions to C2P-RS to improve the predictive vale for response to chemotherapy as Ki-67 reflects the growth fraction and might be complementary to C2P-RS, and GSTP1 is a redox enzyme and confers resistance to chemotherapy.
Patients and Methods: One hundred and ten patients with primary BC (range: 27−73 years, mean: 51.8 years) who were preoperatively treated with weekly paclitaxel (80 mg/m^2, x12) followed by 5-fluorouracil, epirubicin and cyclophosphamide (FEC, 500/75/500 mg/m^2, x4)(P-FEC) between 2004 and 2009 were enrolled in this study. Using the core needle biopsy specimens obtained before NAC, Ki-67 expression was immunohistochemically evaluated, and C2P-RS and GSTP1 expression were measured from tumour lysates. pCR was defined as no invasive foci and no lymph node involvement.
Results: Patients characteristics were as follows: pre-menopausals 46%; Stage IIA 27%, IIB 48%, IIIA 19%, IIIB 5%; histologic grade I 15%, II 64%, III 21%; ER (+) 56%; PR (+) 38%; HER2 (+) 27%. Of 110 patients, pCR was achieved in 19 (17%). The population of each group according to C2P-RS, Ki-67, and GSTP1 were as follows: C2P-RS, high risk 43%, intermediate risk 17%, and low risk 40% at prefixed cutoff values for recurrence prediction; Ki-67, high (>20%) expression 65% and low ($\leqslant$ 20%) expression 35%; GSTP1, high expression 37% and low expression 63% at an optimal cutoff of this cohort. In the analysis of C2P-RS alone, tumours in the high + intermediate risk group were likely to attain pCR compared with those in the low risk group, but the difference was not statistically significant (positive predictive value (PPV) 23%, negative predictive value (NPV) 91%, $P = 0.064$). In the combination analysis of C2P-RS, Ki-67 and GSTP1, however, tumours with high + intermediate risk based on C2P-RS, high Ki-67 expression, and low GSTP1 expression significantly attained pCR compared with others (PPV 43%, NPV 92%, $P < 0.001$). In subset analyses, classification according to these three markers provided significant differences in pCR rates in not only the ER-negative subset (PPV 67%, NPV 86%, $P < 0.001$) but also the ER-positive subset (PPV 25%, NPV 96%, $P = 0.016$).
Conclusions: These results indicate that the combination analysis of C2P-RS with Ki-67 and GSTP1 expressions was able to predict pCR to P-FEC more accurately compared with C2P-RS alone. The combination analysis of these markers may be a useful predictor for response to chemotherapy in both ER-negative and ER-positive BCs.

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First Results From a Study Analyzing CYP2D6 Genotypes and Tamoxifen Metabolites in a Canadian Population With Endocrine Responsive Breast Cancer

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Background: The routine use of commercially available cytochrome P450 2D6 (CYP2D6) genotype testing in patients with endocrine responsive breast cancer on tamoxifen (TAM) treatment has been recently discouraged. Conflicting results in publications regarding the prognostic utility of this test remain unexplained. Confounding factors could be lack of predicted correlation between CYP2D6 genotype and TAM active metabolites, or variability of patient compliance.
Methods: A hypothesis generating pilot study of consecutive, consenting breast cancer patients on tamoxifen was conducted to examine the relationship between genotype, patient-reported treatment adherence and TAM metabolites levels. Patients were genotyped for CYP2D6 polymorphisms using long-range PCR and detection by 1% Agarose gel electrophoresis. Plasma was collected at 1 time point, after at least 6 weeks of treatment with TAM 20 mg daily, to measure TAM, 4-hydroxy N-desmethyl tamoxifen (endoxifen), 4 hydroxy tamoxifen (4OHtam) and N-desmethyl-tamoxifen (NDtam). Levels were determined by High Performance Liquid Chromatography (HPLC) tandem mass-spectrometry. Kruskal Wallis test was used to test association between metabolites ratio/genotype group and active metabolites levels/adherence.
Results: We present results of the first 43 patients enrolled, 40 treated in the adjuvant setting. None were on concurrent CYPD6 inhibitors. Over a 2 week period 26 (60.5%) never missed a TAM dose, 15 (34.9%) missed 1−2 times and 2 (4.7%) >5 times. We found an association between ratios of endoxifen/TAM ($p = 0.023$), endoxifen/NDtam ($p = 0.006$), NDtam/TAM ($p = 0.021$) and genotype. There was also a trend for increased endoxifen levels in the adherent population ($p = 0.06$).

Table 1. Summary of genotype and metabolites levels results

Genotype CYP2D6	Metabolites, mean (ng/ml)			
	UM Ultrametabolizer	EM Extensive metabolizer	IM Intermediate metabolizer	PM Poor metabolizer
	n = 2 (4.7%)	n = 37 (86.0%)	n = 3 (7.0%)	n = 1 (2.3%)
Ztam	4.65	2.45	2.36	2.23
Endox	39.05	20.15	11.21	7.22
TAM	323.50	276.16	264.33	417.00
NDtam	433.50	479.45	597.00	898.00

Conclusions: Our data suggests the predicted association between endoxifen levels and genotype. Results from additional enrolled patients will better confirm the potential important confounding effect of drug adherence.