in independent series this may result in a diagnostic test that could assist in neoadjuvant treatment selection.

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Lymph node ratio is an independent risk classifier in node positive breast cancer patients: results of the phase III BIG 02-98 trial

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Background: The lymph node ratio (LNR), defined as the number of positive nodes divided by the number of examined nodes, has recently been proposed to be a better prognostic factor than the number of positive nodes. We conducted a prognostic analysis of LNR in the BIG 02-98 trial, which evaluated the role of docetaxel in combination or in sequence to doxorubicin as adjuvant treatment of node-positive breast cancer patients.

Methods: The BIG 02-98 trial enrolled 2.887 patients and currently has a median follow-up of 8 years. To be eligible, patients were to have non-metastatic breast cancer, at least one positive axillary node, and a minimum of eight dissected nodes. LNR was evaluated as both a continuous and a categorical variable using predefined cut-offs ($\leqslant$0.2; >0.2 to $\leqslant$0.65; >0.65, which define low, intermediate, and high-risk, respectively) [1]. A multivariate analysis of disease-free survival (DFS) stratified for number of positive nodes and LNR was performed. The magnitude of taxane benefit was estimated for the different LNR categories.

Results: In a multivariate analysis of DFS stratified for the number of positive nodes, LNR was significantly associated with prognosis when included either as a continuous variable (HR 3.30; 95% CI 2.04–5.32) or a categorical variable (LNR >0.65 vs. <0.2, HR 1.80; 95% CI 1.28–2.52). The number of positive nodes was also significantly associated with prognosis in a multivariate analysis of DFS stratified for LNR as a categorical variable (HR 1.08; 95% CI 1.04–1.13). In a multivariate model with both the number of positive nodes and LNR as continuous variables, for every 10% increase in the LNR and for every additional positive node there was an increase in risk of 13% ($p < 0.001$) and 4.4% ($p = 0.55$), respectively. There was larger benefit of taxane therapy in the higher-risk LNR subgroup (LNR > 0.65, HR 0.71; 95% CI 0.54–0.93).

Conclusions: LNR adds prognostic information in node-positive breast cancer. The large number of evaluated nodes ($\geqslant$8) in the BIG 02-98 trial reduces the potential surgical bias of previous series and reinforces the prognostic importance of LNR classification. Taxane benefit in node-positive patients may be larger in the higher-risk LNR subgroup.

References

[1] Vinh-Hung et al, J Clin Oncol 2009; 27: 1062–1068.

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Monitoring serum HER2 levels in the neoadjuvant "Geparquattro" trial − a decrease predicts pathological complete remission

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Background: In the neoadjuvant setting, there is a high need for factors that enable the monitoring of therapy in addition to clinical evaluation. We investigated the predictive value of HER2 serum levels (sHER2) for histopathological response in 175 breast cancer patients undergoing neoadjuvant chemotherapy (NT) within the GeparQuattro trial. The clinical trial GeparQuattro incorporated NT approaches (epirubicin/cyclophosphamide prior to randomization to either docetaxel alone, docetaxel in combination with capecitabine or docetaxel followed by capecitabine) and additional trastuzumab treatment for all patients with HER2-positive tumors.

Materials and Methods: sHER2 levels were measured by a commercially available ELISA in 90 patients with a HER2 positive primary tumour and 85 patients with a HER2 negative primary tumour. sHER2 was measured before initiation of NT and after finalization of NT (pre-surgery). Pathological complete remission (pCR) was defined as no microscopic evidence of invasive residual tumour cells in all resected specimens of the breast and lymph nodes (ypT0ypN0 & ypTisypN0).

Results: ROC-curve analysis revealed that a sHER2 cut-off level of 10 ng/ml has a sensitivity of 72%, a specificity of 85%, a positive predictive value of 85% and a negative predictive value of 73% in discriminating between positive and negative HER2 status. Median pre-chemotherapy sHER2 was significantly higher in patients with pCR compared to patients with no pCR (14.9 ng/ml versus 8.7 ng/ml, $p = 0.001$). In 87 HER2 positive patients, we found a positive significant association between pathological complete remission (pCR) and decrease of sHER2 levels ($p = 0.02$), which was also significant in multivariate analysis (OR = 3.2, 95% CI 1.13–9.55, $p = 0.029$). In 73 HER2 negative patients, we observed no association between change of sHER2 levels and pCR ($p > 0.05$).

Conclusions: The HER2 ELISA is a highly sensitive test to predict HER2 status in breast cancer patients before NT. Results of this study demonstrate pre-chemotherapy sHER-2 levels as well as a decrease of serum levels to be a significant predictor of response to NT for breast cancer. Thus, monitoring sHER2 levels in the presence of trastuzumab treatment might be a promising adjunct to the clinical evaluation during NT in HER2 positive patients.

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Risks of drug interactions with hormonal therapy: incidence of concurrent medications affecting the CYP2D6 enzyme system in breast cancer patients

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Background: Recent literature points to the importance of the CYP2D6 enzyme system in the activation of tamoxifen (tam) to its more active metabolite endoxifen. Pharmacogenomic variability in the CYP2D6 enzyme exists in many ethnic populations, with up to 10% of individuals being poor metabolizers in certain ethnicities. Poor metabolizers are unable to convert tam to endoxifen, resulting in reduced efficacy of tam. Medications that inhibit the CYP2D6 enzyme can mimic the CYP2D6 poor metabolizer pharmacogenomic profile. These well characterized medications (paroxetine, fluoxetine, bupropion) are commonly used in the general population as well as in breast cancer patients. The goal of this project was to observe the incidence of these and other medications that are involved with the CYP2D6 enzyme and develop recommendations for selective pharmacogenomic testing in our breast cancer population.

Materials and Methods: Drug claim data was extracted from the Ottawa Hospital Breast Cancer Disease Site Group clinical database for any patient that was publicly funded by the Ontario Drug Benefit plan. Any patient on hormonal therapy (tam or Aromatase inhibitor [AI]) or CYP2D6 medications (strong to weak inhibitors) were included in the analysis.

	Tamoxifen (N = 154, 29%)		Aromatase inhibitor (N = 321, 60%)		No hormonal therapy (N = 68, 13%)	
	N	(%)	N	(%)	N	(%)
Strong inhibitor						
Bupropion	2	1.3%	2	0.6%	4	5.9%
Fluoxetine	0		8	2.5%	10	14.7%
Paroxetine	5	3.2%	6	1.9%	13	19.1%
Moderate inhibitor						
Sertraline	1	0.6%	6	1.9%	2	2.9%
Weak inhibitor						
Amiodarone	0	0%	3	0.9%	3	4.4%
Venlafaxine	15	9.7%	21	6.5%	24	35.3%
Citalopram	9	5.8%	15	4.7%	19	27.9%
Escitalopram	0	0%	1	0.3%	3	4.4%

Results: 945 patients were identified to have drug claims in the database. Of these patients, 531 (56%) had eligible claims for this analysis. 463 (87%) of these patients received one of the prescribed hormonal therapies while 68 (13%) were not on hormonal therapy but did receive the CYP2D6 medications. 154 patients (29%) received tam; 321 patients (60%) received an AI. 7 patients (4.5%) receiving tam and 16 patients (5%) receiving an AI were concurrently on a strong CYP2D6 inhibitor. One