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

11 Poster discussion

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.

12 Poster discussion

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.

13 Poster discussion

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

patient (0.6%) on tam and 6 patients (1.9%) were receiving an AI with a moderate inhibitor. 24 patients (16.5%) on tam and 40 patients (12.4%) receiving an AI were receiving weak CYP2D6 inhibitors.

Conclusion: While infrequent, breast cancer patients receive medications that can have an adverse effect on tam therapy, primarily its metabolism and activation. Patients receiving AI therapy do receive medications that can interact with tam metabolism, and as such can be a challenge to manage if they have to change from an AI to tam if they cannot tolerate an AI. This is not an infrequent event as our centre has shown that up to 20% of breast cancer patients discontinue AI's due to side effects. Patients are frequently receiving moderate to weak inhibitors of CYP2D6, and these patients should be tested for their pharmacogenomic profile prior to initiating tam to determine if they are wild-type vs intermediate or poor metabolizers.

14 Poster

Influence of zoledronic acid on bone mineral density in premenopausal women with hormone receptor positive or negative breast cancer and neoadjuvant or adjuvant chemotherapy or endocrine treatment

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Background: Depending on baseline bone mineral density (BMD), adjuvant chemotherapy or endocrine therapy of premenopausal breast cancer patients can lead to a substantially increased risk of osteoporotic fractures. Hereby, a significant decrease of BMD > 10% after 2 years of therapy has been reported. Adjuvant therapy with zoledronic acid (Zometa®) in early breast cancer was investigated in the ABCSG-12 and the Zo-Fast trial. Zoledronic acid 4 mg given every six months increased BMD in premenopausal and postmenopausal women receiving endocrine treatment. In addition, a significant increase in PFS could be observed in favor of zoledronic acid.

Material and Methods: The goal of the two monocentric, placebo-controlled, randomized studies Probone I and Probone II is to demonstrate that adjuvant therapy with zoledronic acid improves BMD in premenopausal women. Hormone receptor negative patients (Probone I) are treated with (neo)adjuvant chemotherapy, hormone receptor positive patients (Probone II) with endocrine treatment alone or in combination with (neo)adjuvant chemotherapy. Patients receive zoledronic acid or placebo i.v. every 3 months for 2 years. Primary objective is the change in BMD at the lumbar spine between baseline and month 24 (measured by DXA). Secondary objectives include disease free survival, BMD at total hip and os calcis, BMD measured by QUS at os calcis and phalanges, markers of bone turnover, pathologic fractures, safety and tolerability. BMD is measured at baseline, 12 and 24 months. QUS and markers of bone turnover are measured at baseline, 3, 6, 12 and 24 months.

Results: Recruitment has been finished in 2009 and 71 hormone receptor positive and 11 hormone receptor negative patients have been enrolled into the studies. 30 out of 82 patients have already finished treatment. The design of the study and demographic data of the enrolled patients will be presented.

Conclusion: Probone I/II are two ongoing studies to evaluate the effect of adjuvant zoledronic acid on BMD in premenopausal patients with breast cancer receiving chemotherapy and/or endocrine therapy. The results of these studies will be of great interest for daily practice because of the lack of approved treatments for the prevention of cancer treatment or aromatase inhibitor induced bone loss in patients with early breast cancer.

15 Poster

Five years of exemestane as initial therapy compared to tamoxifen followed by exemestane for a total of 5 years: the TEAM trial, a prospective, randomized, phase III trial in postmenopausal women with hormone receptor-positive early breast cancer

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Background: Exemestane (E) is a steroidal Aromatase Inhibitor (AI) with an established role in early breast cancer after 2−3 years of Tamoxifen (T). Additionally, AIs have shown superiority to T as initial adjuvant therapy. The Tamoxifen Exemestane Adjuvant Multinational (TEAM) study has been prospectively designed to compare the role of E as initial adjuvant therapy with a sequential approach of T followed by E.

Methods: Postmenopausal patients with hormone receptor-positive early breast cancer were randomized to open-label E 25 mg/d or T 20 mg/d. All patients completed surgery and chemotherapy, if indicated. Data were collected and analyzed by the Central Data Center in Leiden, The Netherlands. The trial was initiated in 2001 with the primary objective being a comparison of disease-free survival (DFS) with T vs. E. In 2004, TEAM was modified in response to new data; all those initially receiving T were switched to E after 2.5−3 years. An additional 2500 patients were recruited and randomized at diagnosis to E or T followed by E for 5 years. The modified study design included 2 co-primary analyses: (1) DFS of T vs. E that was previously reported at 2.75 years follow-up and (2) DFS at 5 years follow-up of E vs. T followed by E.

Results: Between 2001 and January 2006, 9779 women were randomized to TEAM. In total, 99% of patients were ER+ and/or PgR+, 50% were node-negative, 44% underwent mastectomy, 68% received radiotherapy, and 36% received chemotherapy. Median follow-up is now 5.1 years. There were 712 DFS events in E vs 714 in T followed by E (locoregional or distant recurrence, second breast cancers, or death without recurrence); HR 0.97 (95% CI 0.88–1.08; p-value 0.60). There were 400 patients with distant metastases in E vs 420 in T followed by E; HR 0.93 (95% CI 0.81–1.07; p-value 0.30). No additional safety issues have emerged with longer follow-up.

Conclusion: Overall this trial shows that starting with E is not more effective than T followed by E in preventing breast cancer recurrence. The previously reported significant improvement in distant recurrence with E vs. T at 2.75 years has not been maintained with longer follow-up after switching from T to E. This suggests that for postmenopausal patients with endocrine sensitive early breast cancer the use of either 5 years of upfront E or T followed by E are appropriate treatment options.

16 Poster

Circulating tumour cells (CTCs) can be detected in peripheral blood of breast cancer (BC) patients two years after primary diagnosis

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Background: Recent trials have demonstrated prognostic relevance of CTCs in metastatic BC. The SUCCESS trial evaluates the role of CTCs at primary diagnosis and after chemotherapy as well as two and five years after diagnosis in primary BC patients treated with chemotherapy and zoledronate.

Methods: We analyzed 23 ml of peripheral blood in N+ and high risk N− primary BC pts receiving 3×FEC (500/100/500)–3×Doc100 q3w vs. 3×FEC (500/100/500)–3×DocGemcitabine (75/1000 d1+8) chemotherapy