metastases was brain in 17.8% of relapsing patients (35% of relapsing patients who received T). The 2 year RFS among patients receiving concurrent chemotherapy + T was 94.7% whereas sequential CT followed by T was 98.4%. In the T treated cohort the 2 year RFS among node negative and node positive patients were 97.8% and 94.4% respectively (p = 0.06). In the cohort of HER-2 positive patients who did not receive T, the 2 year RFS among node negative and node positive patients were 90.7% and 75.5% respectively (p = 0.007). The corresponding 2 year distant RFS in this same cohort was 93.1% and 80.3% respectively (p = 0.01).

Conclusions: A population based analysis of adjuvant trastuzumab use among Canadian women demonstrates highly favorable outcomes at the 2 year follow-up period. Although retrospective in nature, this is one of the first studies to observe breast cancer outcomes in a more generalized population with widespread publicly funded use of T.

8 Poster discussion

Independent prognostic factors for response: updated results of the ABCSG-24 study evaluating the addition of capecitabine to epirubicin-docetaxel neoadjuvant therapy for early breast cancer (EBC)

G.G. Steger[1], R. Greil[2], R. Jakesz[1], A. Lang[3], B. Mlineritsch[2], M. Rudas[1], C. Marth[4], H. Stoeger[5], C.F. Singer[1], M. Gnant[1]. *[1]Medical University of Vienna, Department of Internal Medicine I Division of Oncology, Vienna, Austria; [2]Paracelsus University Salzburg, III Medical Department, Salzburg, Austria; [3]Feldkirch Hospital, Department of Internal Medicine, Feldkirch, Austria; [4]Medical University of Innsbruck, Department of Obstetrics and Gynaecology, Innsbruck, Austria; [5]Medical University of Graz, Department of Oncology, Graz, Austria*

Background: The randomised, phase III ABCSG-24 study evaluated the influence of the addition of capecitabine (C) to 6 cycles of neoadjuvant epirubicin-docetaxel (ED; EDC therapy) on pathological complete response (pCR) rate in patients with EBC. Additional objectives were comparison of the rates of breast conservation (BCR) and axillary lymph node involvement at the time of final surgery. The aim of the current analysis was to assess the role of known risk factors on response to EDC.

Methods: Patients with biopsy proven, operable breast cancer (except T4d), +/− nodal involvement, who were scheduled for neoadjuvant chemotherapy were stratified according to known risk factors (menopausal status, hormone receptor status, tumour grade and stage, HER2 status) and randomised to 6 x ED every 21 days (day 1: E 75 mg/m^2 i.v., D 75 mg/m^2 i.v., day 2: pegfilgrastim 6 mg) +/− C (2 × 1,000 mg/m^2/day for 14 days). The accrual target was 536 patients (94 with HER2-positive disease) to achieve 510 evaluable patients and detect a difference in the rate of pCR of 16% (ED) versus 27% (EDC) with a power of 83% at a significance level of 0.05 (two-sided Chi-squared test). Patients with HER2-positive disease were also randomised to neoadjuvant trastuzumab (T) or placebo.

Results: Baseline characteristics were well balanced between the ED (n = 257) and EDC (n = 255) groups. Median age was 49 years (range 25−73) and 67% and 74% of patients had hormone receptor-negative and HER2-negative tumours, respectively. pCR rate was significantly increased with EDC compared with ED (24.3% vs 16.0%; HR 0.58 [0.38–0.92], p = 0.02). A logistic regression model demonstrated that hormone receptor status (p < 0.001), tumour stage (p = 0.002) grade (p < 0.001), and C therapy (p = 0.03) were independent prognostic factors for pCR. Overall, no significant difference in BCR or rate of axillary lymph node involvement was noted. There was no significant difference in the incidence of serious adverse events (EDC 26% vs ED 21%) and 96% and 94% of patients receiving ED and EDC, respectively, completed all 6 cycles of therapy.

Conclusions: These data indicate that hormone receptor status, tumour stage and grade, and treatment with C are independent prognostic factors for response when C is integrated into a taxane-/anthracycline-based neoadjuvant regimen.

9 Poster discussion

Breast-conserving surgery after preoperative endocrine therapy versus chemotherapy in postmenopausal patients with estrogen-receptor-positive breast cancer

V.F. Semiglazov[1], V.V. Semiglazov[1], G.A. Dashyan[1], A.G. Manikhas[2], E.K. Ziltsova[1], A.A. Malodusheva[1], V.G. Ivanov[1], R.V. Donskih[1], R.M. Paltuev[1], A.E. Kletsel[3]. *[1]N.N. Petrov Scientific Research Institute of Oncology, Breast Cancer, St-Petersburg, Russian Federation; [2]City Oncological Hospital, Breast Cancer, St-Petersburg, Russian Federation; [3]Hospital Gross-Umstadt, Breast Cancer, Frankfurt-Main, Germany*

Background: Neoadjuvant therapy may increase the proportion of women eligible for beast-conserving surgery (BCS) by reducing tumor size. Endocrine therapy and chemotherapy have been investigated in this setting.

Methods: A total of 239 patients (pts) with ER-positive and/or PgR-positive breast cancer (T2N1−2, T3N0−1, T4N0M0) were randomly assigned to receive neoadjuvant endocrine therapy (ET) [anastrazole 1 mg/day or exemestane 25 mg/day for 3 months, 121 patients] or chemotherapy (CT) [doxorubicin 60 mg/m^2 with paclitaxel 200 mg/m^2, four 3-week cycles, 118 patients]. All pts were considered to be ineligible for BCS at enrollment. After BCS all pts received radiotherapy (50 Gy in 25 fractions). The median follow-up time was 5.6 years.

Results: The primary efficacy end point was already reported (Cancer 2007; 110: 244−54). Overall response (OR=CR+PR) was similar in the ET group (65.5%) compared with CT (63.6%; p > 0.5).

After completing neoadjuvant treatment, 31 (13%) patients did not undergo surgery: 12.3% of pts who were receiving ET and 13.5% of pts who were receiving CT. Progressive disease was observed in 9% of pts who were receiving ET and 9% of pts who were receiving CT (p > 0.5). There was a trend toward higher overall rates of objective response (OR) and BCS among patients with tumors expressing high levels of ER (Allred score >6) in the ET group compared CT (p = 0.054; 43% vs 24% respectively). There was no significant difference between ET and CT relative to the incidence of locoregional recurrences and distant metastases (7.9% and 7.3%, p = 0.99; 14.8% and 15.2%, p = 0.83, respectively).

There was no significant difference in DFS through 5 years of follow up between the 121 pts who received neoadjuvant ET and 118 women who received CT: 71.0% and 67.7% (p > 0.5).

Fifty one (43%) pts who were receiving CT experienced neutropenia (grade 2−4) that led to treatment interruption. ET was well tolerated.

Conclusion: For elderly postmenopausal women with comorbid conditions and large hormone-responsive tumors (ER+ or PgR+) BCS may be possible after well-tolerated, preoperative ET with aromatase inhibitors less toxic than CT.

10 Poster discussion

Homologous recombination deficiency in breast cancer and association with response to neo-adjuvant chemotherapy

E.H. Lips[1], L. Mulder[1], J. Hannemann[1], M.J. Vrancken Peeters[2], M.J. van de Vijver[3], J. Wesseling[3], P.M. Nederlof[3], S. Rodenhuis[4]. *[1]Netherlands Cancer Institute − Antoni van Leeuwenhoek hospital, Experimental Therapy, Amsterdam, The Netherlands; [2]Netherlands Cancer Institute − Antoni van Leeuwenhoek hospital, Surgical Oncology, Amsterdam, The Netherlands; [3]Netherlands Cancer Institute − Antoni van Leeuwenhoek hospital, Pathology, Amsterdam, The Netherlands; [4]Netherlands Cancer Institute − Antoni van Leeuwenhoek hospital, Medical Oncology, Amsterdam, The Netherlands*

Background: Tumors with homologous recombination deficiency (HRD) are highly sensitive to DNA double strand break (DSBs) inducing agents, including alkylating agents and poly (ADP-ribose) polymerase (PARP)-inhibitors. BRCA1- and BRCA2- associated tumors, which are thought to be HRD, may be identifiable employing an array Comparative Genomic Hybridization (aCGH) classifier. As this classifier was primarily developed to recognize breast cancers in BRCA mutation carriers, we determined these profiles together with several other HRD characteristics in sporadic cancer patients and correlated the presence to neoadjuvant treatment response to DSB inducing chemotherapy.

Material and Methods: Forty-three triple negative (TN) and 91 estrogen receptor positive/HER2− (ER+/HER2−) pre-treatment biopsies were examined, procured from sporadic breast cancer patients scheduled to receive neoadjuvant therapy with doxorubicin/cyclophosphamide. aCGH for assessing BRCA1-like and BRCA2-like profiles was performed. In addition, BRCA1 promotor methylation, BRCA1 mRNA expression and amplification of the EMSY gene were assessed. Response to neoadjuvant treatment was assessed by measuring pathological complete remission (pCR) and near pCR at the time of surgery.

Results: Inactivation of BRCA1 was frequent in TN tumors: 54% of these tumors showed a 'BRCA1-like' profile at aCGH. BRCA1 promotor methylation and reduced BRCA1 mRNA expression were observed in 25% and 43% of the TN tumors, respectively. Although a slightly higher treatment response was seen in TN tumors with a BRCA1-like profile, this was not significant (70% vs. 42%, p = 0.231). In ER+ tumors, a BRCA2-like profile and the amplification of the BRCA2 inhibiting gene EMSY were frequently observed (37% and 15% respectively). A BRCA2-like profile was associated with a significantly higher response rate (35% vs 12%, p = 0.033). EMSY amplification and a BRCA2-like profile occurred together in only one case. EMSY was not associated with treatment response, questioning the role of EMSY in HRD.

Conclusion: Abnormalities associated with BRCA1 inactivation are present in about half of the TN breast cancers and may identify tumors that are sensitive to chemotherapy that causes DNA DSBs. In ER+/HER2− tumors, the BRCA2-like profile may indicate HRD and thus be predictive for benefit from new targeted agents, involved in DNA repair. After validation

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

O. Metzger[1], E. de Azambuja[2], E. Quinaux[3], P. Francis[4], M. Buyse[3], J. Crown[5], M. Andersson[6], A. Di Leo[7], M. Piccart-Gebhart[8]. [1]*Institut Jules Bordet, Clinical and Translational Research, Brussels, Belgium;* [2]*Institut Jules Bordet and Université Libre de Bruxelles (U.L.B), Medical Oncology Clinic, Brussels, Belgium;* [3]*International Drug Development Institute, Biostatistics, Louvain-La-Neuve, Belgium;* [4]*Peter MacCallum Cancer Centre and St Vincent's Hospital, ANZ BCTG and IBCSG, Melbourne, Australia;* [5]*St. Vincent's Hospital and Irish Clinical Oncology Research Group, Breast Committee, Dublin, Ireland;* [6]*The Finsen Centre Copenhagen University Hospital Rigshospitalet, Department of Oncology, Copenhagen, Denmark;* [7]*Sandro Pitigliani Medical Oncology Unit Hospital of Prato, Medical Oncology Clinic, Prato, Italy;* [8]*Institut Jules Bordet and Université Libre de Bruxelles (U.L.B), Medicine Department, Brussels, Belgium*

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

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12 Poster discussion

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

I. Witzel[1], V. Müller[1], S. Loibl[2], T. Fehm[3], G. von Minckwitz[4], H. Eidtmann[5], U. Conrad[6], M. Roller[4], C. zu Eulenburg[7], M. Untch[8]. [1]*University Hospital, Gynecology, Hamburg, Germany;* [2]*Hospital of the Johann Wolfgang Goethe-University, Gynecology and Obstetrics, Frankfurt, Germany;* [3]*University Hospital, Gynecology and Obstetrics, Tübingen, Germany;* [4]*German Breast Group, Forschungs GmbH, Neu-Isenburg, Germany;* [5]*University Hospital, Gynecology and Obstetrics, Kiel, Germany;* [6]*St. Barbara Hospital, Obstetrics and Gynecology, Hamm Heesen, Germany;* [7]*University Hospital, Biometrics and Statistics, Hamburg, Germany;* [8]*HELIOS Hospital Berlin-Buch, Gynecology and Obstetrics, Hamburg, Germany*

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

S. Hopkins[1]. [1]*The Ottawa Hospital Regional Cancer Centre, Pharmacy, Ottawa, Canada*

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