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Giving to Women with Metastatic Breast Cancer a Choice Between Oral or Intravenous Chemotherapy: Which the Patient Preference? a Prospective Analysis Focused On Quality of Life and Compliance Through Two Consecutive Phase II Trials

R. Palumbo[1], A. Bernardo[1], A. Riccardi[2], F. Sottotetti[1], C. Teragni[2], B. Tagliaferri[1], G. Bernardo[1]. [1]*Fondazione Salvatore Maugeri, Medical Oncology II, Pavia, Italy;* [2]*Fondazione Salvatore Maugeri, Department of Medical Oncology University of Pavia, Pavia, Italy*

Background: Our Group had previously reported results of two parallel consecutive phase II trials in women with HER2-negative metastatic breast cancer (MBC) given full-oral chemotherapy (CT) with vinorelbine (VNR) and capecitabine (CAP) in combination (Trial A) or Trastuzumab plus i.v./oral VNR in patients with HER2-positive disease (Trial B). Here we present the final results of the prospective analysis focused on patient preference, treatment compliance and quality of life (QoL).

Patients and Methods: Overall, 188 patients have been treated and evaluated. QoL was assessed every two cycles using the EORTC QLQ-BR23 questionnaires. Patient's preference was evaluated using a 10-item questionnaire designed to measure the women opinion and perception regarding oral *versus* intravenous treatments. To investigate treatment tolerability both the patient and physician were asked to quantify their opinion as insufficient-satisfactory-good and very good (score 0 to 3).

Results: All but two patients returned the completed modules at the start of each CT cycle. Over 90% of patients and physicians rated the tolerability of full oral regimen (Trial A) or osVNR/Trastuzumab as 'very good' or 'good' throughout the treatment, with a slight higher physician-detected score. An improvement in tolerability was reported by 92% of patients from their last therapy to present CT: median scores changed from 1 to 2 in 41% and from 2 to 3 in 45% of cases, respectively. Tolerability at 4^{th} and 6^{th} cycle was also positively associated with better progression-free-survival ($p = 0.02$). A statistically significant difference was observed regarding some aspects of QoL, as body image ($p = 0.02$), sexual functioning ($p = 0.01$) and future perspectives ($p = 0.03$). Oral treatment was perceived as advantageous by 98.5% of women, because of reduced hospital admissions (73.8%) and feeling of 'freedom' deriving from the home-based therapy (16.6%).

Conclusions: Our data confirm the good compliance of oral CT, both as *all-oral* combination (VNR/CAP) or associated with Trastuzumab (osVNR/Trastuzumab) as first-line treatment in women with MBC. The most interesting findings were the observed beneficial effect of oral CT on sexual functioning and the significant impact of each degree of improvement in tolerability on the clinical outcome. We believe that by giving the patients a choice between oral or i.v. treatment, patients often sense a feeling of control over the treatment and thereby a control over their life.

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Implementation of Palliative Care in German Breast Centers ñ First Results of a National Questionnaire

R. Wuerstlein[1], J. Uellenberg[2], J. Gaertner[3], P. Mallmann[4], R. Voltz[3], N. Harbeck[5], AG ZBZ (Arbeitsgemeinschaft Zertifizeirter Brustzentren) Germany. [1]*University of Cologne CIO and LMU Munich, Cologne/Munich, Germany;* [2]*University of Cologne CIO, Cologne, Germany;* [3]*University of Cologne CIO, Palliative Care, Cologne, Germany;* [4]*University of Cologne CIO, ObGyn, Cologne, Germany;* [5]*University of Cologne CIO and LMU Munich, Cologne/Munich, Germany;* [6]*in cooperation, Germany, Germany*

Background: In Germany, the majority of breast cancer cases are treated at breast centers (BC) which are certified according to the German Society of Senology and Cancer Society. At the Center of Integrated Oncology (CCC) Cologne-Bonn including its BC, early integration of palliative care (PC) is a clinical and scientific hallmark. Yet, the logistics of actual PC integration into metastatic breast cancer (MBC) care at other centers are not well documented. In view of the encouraging data from NSCLC demonstrating the benefits of early integration of PC, this topic has become increasingly important.

To gain some structural information about the degree and concept of PC integration, a questionnaire to assess the available PC infrastructure was distributed to all certified German BC.

Materials and Methods: We used the national AGZBZ Email-distribution and mail system to contact all directors of officially certified BC in Germany (June 2011: 207). The questionnaire contains 10 questions defined by our interdisciplinary team and assesses the available infrastructure of the center (availability of yearly follow up data, implementation of an interdisciplinary tumorboard for MBC, application of systemic treatment in the department of gynecology or oncology) as well as the availability of specialised PC (in- and outpatient PC, home palliative and hospice care, interdisciplinary approach, pain management). The questionnaire also gives the opportunity to provide comments (as free text) concerning the integration of PC.

Results: The number of patients with MBC treated per year in the BC in an interdisciplinary approach spreads from 0 to 500. In more than 20% there are no PC beds available at the BC or the hospital. In about 40% there is no PC available for outpatient needs. The actual integration of PC in the MBC occurs rather late (only in 23% integration of PC takes place at the time of diagnosing MBC, in more than 70% PC is involved for dying patients only).

Conclusion: Infrastucture and concepts for integrationof PC into MBC therapy are still scarce and vary extremely in quality and quantity. This highlights the need for institutional guidelines and an interdisciplinary consensus on the national level.

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Primary Tumor in Breast Cancer and Its Phenotype in Positive Lymph Nodes and Later Disease Recurrence (metastatic Breast Cancer): Results of the PRIMET-trial (WSG/DETECT)

R. Wuerstlein[1], M. Freudenberger[2], L. Wildenburg[3], M. Ortmann[4], C. Liedtke[5], O. Gluz[6], R. Kates[7], T. Fehm[8], U. Nitz[6], N. Harbeck[9]. [1]*University Hospital Cologne CIO and LMU Munich, Cologne/Munich, Germany;* [2]*University Hospital Cologne CIO, Cologne, Germany;* [3]*University Hospital Cologne CIO, Cologne, Germany;* [4]*University Hospital Cologne CIO, Pathology, Cologne, Germany;* [5]*University Hospital Muenster, Muenster, Germany;* [6]*Evangelisches Krankenhaus Bethesda, Moenchengladbach, Germany;* [8]*University Hospital Tuebingen, Tuebingen, Germany;* [9]*University Hospital Cologne CIO and LMU Munich, Cologne/Munich, Germany*

Background: For various and unknown reasons, tumor phenotype changes in ER/PR expression and or HER 2 status overexpression between primary tumor (PT) and disease recurence (DR) in the course of disease. The clinical relevance of this possible changes between PT, lymph nodes (LN) at the time of primary breast cancer (BC) and recurrence remains unclear. In PRIMET we evaluate discordance rates between PT, LN and DR to find predictors for patient outcome and to establish a database and tumorbank for further analysis.

Materials and Methods: PRIMET is a prospectively planned, retrospective multicenter quality assurance study comapring BC phenotype in PT, its corresponding LN and DR. Included were patients of 11 centers in Germany, from the WSG trial group and the DETECT group, with BC diagnosed first from the early 1980s to 2010. Patients with unilateral BC with subsequent/synchronous local-regional and/or distant DR were included. A systemic chart review and in Cologne a LN subprotocol with central pathology was performed.

Results: 436 patients were entered into PRIMET. 414 had no evidence of a primary metastatic disease (M0). Median follow-up in patients alive at time of analysis (Oct 2010) was 73.1 months. Median disease free survival (DFS) was 45.1 months. Triple receptor status for PT and DR was available in 377 patients. Discordance rates were seen in 22% for ER, in 30% for PR and 22% for HER 2 status. Significant differences regarding post recurrence survival (PRS) and DFS were observed with persistent triple negative breast cancer (TNBC) being associated with particularly low DFS and PRS. In a subset of patients ($n = 20$) tumor phenotype was analysed in corresponding LN at primary diagnosis. In 60% of those cases discordance regarding triple receptor expression was observed with a majority in difference between PT and LN.

Conclusions: The results of PRIMET show that the triple receptor status of PT and DR are associated with DFS and PRS. We provide evidence regarding phenotype changes in PT, LN and DR and its prognostic relevance. This confirms the national and international guidelines for re-verification of immunohistochemical status of PT, LN and DR.

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Efficacy of Aromatase Inhibitors in Male Breast Cancer ñ a Single Centre Experience

R. Stevens[1]. [1]*Velindre Cancer Centre, Clinical Oncology, Cardiff Wales, United Kingdom*

Background: Male breast cancer is a rare cancer representing approximately 1% of all breast cancer cases. No randomised data exists to guide treatment. This case series shows the experience of 16 men treated with aromatase inhibitors for locally advanced or metastatic breast cancer in a single centre.

Materials and Methods: This is a retrospective review of all male breast cancer patients referred to Velindre Cancer Centre between 1997 and 2011.

Results: 64 patients were referred to Velindre Cancer Centre over the 14 year period.

Of these, 8 had inoperable or metastatic disease at presentation and a further 17 developed locally advanced or metastatic disease.

16 received an aromatase inhibitor. (9 anastrazole, 5 letrozole, and 2 exemestane).

13 patients received tamoxifen prior to an aromatase inhibitor. 15 patients received AI as either a first or second line therapy.

Duration of AI therapy was assessable in 14 patients. The median duration of aromatase inhibitor therapy was 17 weeks (1−90 weeks) and 6 patients (43%) remained on therapy beyond 24 weeks.

7 patients (47%) on AI had no documented clinical or radiological benefit and had therapy discontinued at the first review.

When comparing those who had a documented response to AI compared with those who never responded, responders were older (median age of 72.5 years (95% CI 69.9–75.1) vs. 64 years (95% CI 59.3–68.7)) and more likely to have recived prior anthracycline based chemotherapy (37.5% vs 14%).

Conclusions: Response rates to aromatase inhibitors in men are lower than would be expected in a similar population of women. Women receiving anastrazole after tamoxifen had a median time to progression is reported as 21 weeks compared to 17 weeks in our cohort (Buzdar 2001). 43% of patients were felt never to have had a clinical or radiological response to AI.

More clinical studies are required to establish why some male breast cancer patients respond to AI but the differences between responders and non-responders suggest testicular function may play a role.

Testicular function is known to decrease with age and patients responding to AI were older on average and a greater percentage of patients responding to AI had prior anthracycline chemotherapy. This case series supports the use of aromatase inhibitors in selected male breast cancer patients but there is still a need for further research into the cellular mechanisms of male breast cancer and the role of testicular steroid hormone production in AI resistance.

References

Buzdar, et al 2001 Phase III, Multicenter, Double-Blind, Randomized Study of Letrozole, an Aromatase Inhibitor, for Advanced Breast Cancer Versus Megestrol Acetate. Journal of Clinical Oncology 19(14): 3357−66.

Thursday, 22 March 2012 12:30–13:30

POSTER SESSION

Molecular Biology, Tumour Biology and Immunology

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MMP11 Expression Increases During Progression of Breast Cancer

T. Fehm[1], S. Schultz[1], K. Sotlar[2], K. Petat-Dutter[2], M. Bonin[3], S. Poths[3], H. Seeger[1], D. Wallwiener[1], H. Neubauer[1]. [1]*University of Tuebingen, Department for Gynecology and Obstetrics, Tuebingen, Germany;* [2]*Ludwig-Maximilians-University Munich, Institute for Pathology, Munich, Germany;* [3]*University of Tuebingen, Microarray Facility Tuebingen, Tuebingen, Germany*

Background: The ductal carcinoma *in situ* (DCIS) of the breast is considered to be the pre-invasive form of the invasive duct carcinoma (IDC). The aim of this project is (1) the identification and validation of potential progression markers and (2) to identify markers for high risk DCIS with aggressive potential. MMP11 (matrix-metalloproteinase 11) is a marker for the transition from DCIS to IDC. It is associated with tumour cell invasion and a poor clinical outcome.

Material and Methods: 15 formalin fixed and in paraffin embedded (FFPE) tissue samples with a 'pure' DCIS without IDC component (patients were at least five years free of cancer), and 15 paraffin tissue samples with DCIS/IDC tumours were selected. Tissue sections were prepared, stained with hematoxylin-eosin and the epithelial cells were isolated by laser capture microdissection (LCM). 200 ng RNA were extracted, hybridized to the Whole Genome DASL Array (Illumina) and bioinformatically evaluated. The RNA was linear amplified using the Ribo-SPIA® technology (WT-Ovation™ FFPE System, NuGen™) and the validation was done by qRT-PCR using the LightCycler® 480 System (Roche).

Results: We were able to identify 993 transcripts that are differentially expressed between DCIS and IDC of the same tumour and 1138 transcripts which are differentially expressed between 'pure' DCIS and DCIS/IDC tumours. Differential expression was validated for 9 transcripts using two sample sets, the technical validation sample set (15 DCIS/IDC tumours, 15 'pure' DCIS) and an independent validation sample set (26 DCIS/IDC tumours, 17 'pure' DCIS). MMP11 is highly expressed in IDC and moderately expressed in DCIS with IDC component. In 'pure' DCIS less or no expression of MMP11 was determined.

Conclusions: We identified progression-specific candidate transcripts using LCM and microarray analysis from FFPE breast cancer tissues. MMP11 is a progression marker which differentiates between high and low risk DCIS.

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Computational Prioritization of NsSNP's Involved in Causing Breast Cancer in Human

A. Kumar[1]. [1]*VIT University, School of Biosciences and Technology, Vellore, India*

Breast cancer is counted among the most common invasive and fatal cancer's in women. It has been reported to cause 458,503 deaths worldwide in year 2008. Therefore the in-depth scientific research is important to gain complete information regarding the molecular pathway related to this disease and to discover the effective pharmacological treatment. We used computational approach to identify the SNPs involved in causing breast cancer. In order to identify the possible locus of tumorigenic mutations we analyzed 535 nsSNPs in 20 candidate genes (BRCA1, BRCA2, CDH1, CHEK2, DIRAS3, ERBB2, MYC, CCND1, TRIM37, APPBP2, TRAP240, RAD51C, BCAS3, PTEN, STK11, TP53, AR, ATM, RB1CC1, AKT1, BARD1, PALB2, RAD51L1, NQO1, NQO2, RAF1, ZNF217, TGFB1, TOX3, CYP1A1, CASP8, HMMR, LSP1, RAD51 and MAP3K1) taken from journals and publications based on the case control studies. Using evolutionary conservation analysis and statistical potential energy function evaluation algorithm we prioritized 171 SNPs that were predicted to be damaging. Further using Support Vector Machine based classifier we selected 63 nsSNP's that were reported to be extremely deleterious and could be the possible cause of inducing cancers in human breast region. Among these 63 variants 12 were reported to distrupt the lignad binding site and 7 lead to the overpacking at the burried regions. Molecular Dynamic Simulation of native and mutant proteins were carried out to analyze the structural dependency of the mutants tumorigenic property. The clear variation in the RMSD (Root Mean Square Deviation) values were observed in all the 19 variants which accounts for the loss of proper signal transdution in the cellular pathways which may induce the oncogenicity leading to Cancer. To study the pathway based dependencies of these mutations we used Ordinary Differential Equation and Boolean Algebra to understand the mutation induced relative variation in the rate of activation of phosphorylases and kinases mediated cell divisons. Genetic algorithm is used to predict the unknown concentration of the involved proteins, ligands and enzymes in the native and mutant pathway conditions. These findings will facilitate the understanding of the involvement of nsSNP's in causing breast cancer in human.

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Mitochondrial DNa Mutations and Copy Number Alteration in Breast Cancer Patients From Romania

C. Rusanu[1], A. Botezatu[1], I. Iancu[1], I. Huica[1], A. Plesa[1], G. Anton[1]. [1]*"Stefan S. Nicolau" Institute of Virology, Molecular Biology, Bucharest, Romania*

Background: Breast carcinoma is one of the most common types of malignancy worldwide and the leading cause of mortality from cancer among Romanian women. Mutations in mitochondrial DNA (mtDNA) as well as alterations in mtDNA content have been reported in numerous cancers examined. However, it still remains unclear whether the alterations in mtDNA are related to the clinicopathological features and/or the prognosis in breast cancer.

Material and Methods: Total DNA (nuclear and mitochondrial) was isolated (High Pure PCR Template, Roche Diagnostics) from breast cancer and paired normal breast tissues originating from 40 Romanian patients. Somatic mutations in the D-loop region (4,977-bp deletions) were investigated using Mutector mtDNA kit (TrimGen Corporation). MtDNA copy number was quantified using a one-step quantitative multiplex real-time PCR. A FAM labeled probe and primers were used to amplify the mtDNA sequence of the ATP 8 gene, and a VIC labeled probe and primers were designed to amplify the beta-globine gene.

Results: MtDNA copy number in stage I breast cancer patients was significantly lower than in other stages ($P = 0.0015$). A reduced mtDNA copy number was found often in post menopausal cancer group ($P = 0.024$). The study revealed no difference in mtDNA content related to age ($p = 0.255$) or lymph node involvement ($p = 0.173$).

We failed to detect any mtDNA mutations in normal breast tissue specimens. 16.66% of stage I breast cancer patients presented mutations in D-loop region whereas 28.57% of stage II cases showed mutations in mtDNA. 4,977-bp deletions were detected in 66.66% cases of stage III cancer cases.