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Organized by J. Sehouli and W. Lichtenegger, Department of Gynecology and Obstetrics, Charité, Medical University Berlin, Germany

Poster Abstracts

1
DETECTION OF DISSEMINATED TUMOR CELLS IN PERIPHERAL BLOOD OF PATIENTS WITH OVARIAN CANCER

I. Alpers[1], S. Mahner[2] and B. Brandt[1]
[on behalf of the EU OVCAD consortium[3]]

[1]Institute of Tumor Biology, Center of Experimental Medicine, University Medical Center Hamburg-Eppendorf; [2]Department of Gynecology, University Medical Center Hamburg-Eppendorf, Germany;
[3]EU- Project LSHC-CT-2005-018698 "OVCAD: Ovarian Cancer – Diagnosis of a Silent Killer"

Tumor cell dissemination is a common phenomenon in solid tumors at the time of primary diagnosis. The disseminated tumor cells are thought to be derived from the primary tumor and are potential precursors of metastatic disease. In general ovarian cancer is diagnosed in advanced stages, therefore the standard treatment requires a debulking surgery followed by an aggressive chemotherapy (platinum- and taxane-based therapy). Currently, there is a lack of parameters for an early indication of therapy failure. One potential approach for the development of such parameters could be the isolation and characterization of disseminated tumor cells from peripheral blood of patients with ovarian cancer. For the isolation of disseminated tumor cells from peripheral blood (15-30 ml) a cell enrichment method has been established and characterized, consisting of a density gradient centrifugation and an immunomagnetic cell separation. Blood samples of 49 ovarian cancer patients with local recurrence and of 66 patients with primary ovarian cancer were analyzed. In 8 (16.33%) out of 49 ovarian cancer patients with local recurrence disseminated tumor cells (cytokeratin positive and CD45 negative cells) were detected. Additionally in one blood sample, a cytokeratin positive and CD45 negative cell cluster were found. In blood samples of patients with primary ovarian cancer, 4 (6.06%) out of 66 was identified had disseminated tumor cells and in one sample a cell cluster. The identification and further characterization of disseminated tumor cells of patients with ovarian cancer might contribute to a deeper understanding of the mechanisms of metastasis and might lead to the establishment of new parameters for an early estimation of therapy success and provide a valuable tool for diagnostic and therapeutic approaches.

Key Words: Gynecologic oncology, abstracts, NOGGO.

2
IMPORTANCE OF CA-125 IN ADVANCED FIGO-STAGES IN OVARIAN CANCER

C. Bachmann[1], J. Bachmann[3], A. Staebler[2], E.M. Grischke[1], D. Wallwiener[1] and E.F. Solomayer[1]

Departments of [1]Gynecology and [2]Pathology, University of Tübingen;
[3]Department of Surgery, Technische Universität München, Munich, Germany

Introduction: CA-125 is the most important marker in ovarian cancer. High CA-125 levels are often associated with advanced FIGO- stages and are prognostic factors for relapse. This paper addresses the question of whether CA-125 is a good factor for preoperative evaluation of FIGO- stage and resection status *Aim:* The aim of this study was to evaluate if preoperative CA-125 levels show a correlation with tumor stage. Furthermore, whether this marker is a prediction factor of prognosis, resection status and risk of relapse was also investigated. *Patients:* Between 01/2000 and 06/2007 271 patients with primary ovarian cancer underwent surgery at the

department of Gynecology and Obstetrics at the University Hospital, Tübingen. All patients received surgical staging or tumor debulking as clinically indicated and preoperative CA-125 level was measured. The histological diagnosis was classified in FIGO- stages. CA-125 levels were classified in 3 groups (<35U/l; 35-500U/l; >500U/l). After operation the patients were treated with a standard platinum-based chemotherapy or in current therapy-studies. Of these patients the data of 213 were evaluated, since 58 patients were excluded because they were lost to follow-up. All patients gave their informed consent for data acquisition. The mean follow-up time was 53.5 months. *Results:* A positive correlation could be seen between increased levels of CA-125 and FIGO- stage. In FIGO I CA-125- levels were between 18 and 131 U/l (median 66), in FIGO IV CA-125 levels were between 274 and 2339 U/l (median 957). No patient in early stage (FIGO I/II) showed CA-125>500 U/l. Increase of grading showed higher CA-125 levels. Good correlation could be seen between resection status and CA-125. All patients with CA-125<35 U/l got R0- resection and a significant decrease of the R0- resection rate was seen for higher CA-125, levels (<0.001), 20.5% of patients with CA-125> 500 U/l got R0- resection. Serous cancers showed in 93% CA-125 levels above 35 U/l. In advanced stages there was a significant influence on OAS and DFS for higher CA-125 levels. Independent of FIGO- stages patients with CA-125<35 U/l showed significant longer survival than patients with levels over this limit. *Conclusion:* Increase of CA-125 was seen in advanced stages. High levels of CA-125 show a decrease of the R0- resection rate. Negative influence on OAS and DFS was seen with higher CA-125 levels.

3

PROGNOSTIC VALUE OF SERUM AND ASCITES LEVELS OF ESTRADIOL, FSH, LH AND PROLACTIN IN OVARIAN CANCER

Frank Chih-Kang Chen, Gülten Oskay-Özcelik, Kai J. Bühling, Uta Köpstein, Monika Mentze, Werner Lichtenegger and Jalid Sehouli

Department of Gynecology and Obstetrics, Charité University Medicine Berlin, Campus Virchow-Klinikum, Berlin, Germany

Aim: To investigate the influence of sex hormone levels on tumor biology and patients' outcome in ovarian cancer. *Patients and Methods:* One hundred and six patients with ovarian cancer were enrolled into this prospective study. Serum and ascites samples were obtained intraoperatively. Concentrations of estradiol, FSH, LH and prolactin were measured and correlated with parameters of tumor biology, such as FIGO stage, tumor spread and postoperative tumor residual mass. Patients with primary ovarian cancer were compared to patients with recurrent disease. Influence factors on progression-free survival and overall survival were analyzed using the Kaplan-Meyer method. *Results:* Serum FSH concentrations were significantly higher and estradiol concentrations in ascites were significantly lower in patients with recurrent disease. According the multivariate analysis, only FSH level in ascites was seen to be an independent prognostic factor for patients' survival. *Conclusion:* High level of FSH in the ascites provides prognostic information in patients with ovarian cancer and is inversely correlated with patient's survival.

4

MULTICENTER STUDY ON THE DETECTION OF DISSEMINATED TUMOR CELLS IN PRIMARY NODE-POSITIVE BREAST CANCER

K.E. Effenberger[1], E. Borgen[2], C. Eulenburg[1], A. Grosser[1], M. Synnestvedt[2], R. Kaaresen[3], J.M. Nesland[2], K. Pantel[1] and B. Naume[2]

[1]University Medical Center Hamburg-Eppendorf, Germany;
[2]Rikshospitalet, University of Oslo;
[3]Ullevaal Hospital, Oslo, Norway

Detection of disseminated tumor cells (DTC) in bone marrow (BM) has prognostic value in primary breast cancer (BC). Anti-cytokeratin (CK) antibodies (Abs) have been established as detection markers. Here, a direct comparison of two well-established Abs is presented. BM of 65 N+ BC patients (M0, pT1-3, pN1-3) were screened. For each patient 2×10^6 cells were analyzed per Ab, using A45-B/B3 (A45) and AE1/AE3 (AE) Abs in parallel. Two cell scorings were carried out and compared for both Abs independently, called "Oslo"- and "HH"-scoring. Eight out of 65 (12.3%), and 13/65 patients (20.0%) were BM+ for A45 and AE, respectively. Concordance obtained for the two Abs was 73.9% for the Oslo- and 80.0% for the HH-scoring (p=0.044). Comparison of the two different scorings for A45 and AE analysis each revealed a highly significant correlation (p<0.001). AE- and A45-positive BM were found more frequently in tumors of higher grading, and for AE also in hormone receptor (HR) negative patients. Grouped analysis showed a significant correlation for grading and "AE and/or A45 positive" by HH-scoring as well as "AE Oslo and/or HH positive". Survival analyses revealed worse prognoses for each Ab and for each of the observers. Combined analyses displayed the same; AE and/or A45-positive patients had a significantly higher mortality risk applying Oslo- (p=0.023) or HH-scoring (p=0.049). Results indicate that two frequently used Abs for DTC detection do not give identical results. The

concordance between the two scorings is high but does not lead to identical conclusions. Combined analysis appears to be superior which might imply the parallel use of these Abs in DTC diagnostics. To verify these data, a larger cohort of patients will be analyzed.

5

METASTATIC BREAST CARCINOMA CELLS EXPRESS A VARYING PATTERN OF CYTOKINES AND INDUCE A SPECIFIC PRO-INFLAMMATORY TUMOUR MICROENVIRONMENT

C. Loebel[1], S. Huwe[1], E. Fieber[1], A. Steinborn[1], P. Brodt[2], C. Sohn[1] and M. Eichbaum[1]

[1]University of Heidelberg Medical School, Heidelberg, Germany;
[2]Royal Victoria Hospital, McGill Cancer Center, Montreal, Canada

Introduction: New findings suggest fascinating parallels between the pathophysiology of inflammation and the progression of malignant solid tumours. Resident macrophages induce a specific local microenvironment by secreting TNF-α and other cytokines and therefore appear to play a key role in these mechanisms. A pro-inflammatory microenvironment promotes the formation of hepatic metastases. Of particular interest is the ability of mammary carcinoma cells to stimulate macrophages by induction of a tumour-promoting environment and therefore expression of a particular pattern of cytokines. *Materials and Methods:* Four metastatic human breast cancer cell lines (ZE, KM22, 1590, SKBR-3) as well as a human mammary epithelial cell line were cultured under standardised conditions. After incubation at 37°C for four days their supernatants were harvested. Using a Human Cytokine Antibody Array (RayBio®), which allows the detection of 42 different pro-inflammatory cytokines, the supernatants were analysed for secreted cytokines semiquantitatively. Strongly expressed cytokines were quantified using ELISA. *Results:* All investigated breast cancer cell lines showed an individual pattern of inflammatory cytokines of which IL-8 and MCP-1 were particularly strongly expressed by all tumour cells. Furthermore a strong secretion of IL-6, ENA-78, GRO and RANTES could be observed in an individual manner. High concentrations of IL-6 were detected in KM22 (21384 pg/ml). MCP-1 as well as RANTES were strongly expressed by 1590 (237.6 pg/ml; 797,6 pg/ml). On the contrary human mammary epithelial cells showed a considerable expression of IL-8, GRO and GRO-α. *Conclusion:* Human breast carcinoma cells secrete pro-inflammatory cytokines in a certain manner. Using those different patterns they induce a specific pro-inflammatory microenvironment. By contrast human mammary epithelial cells secrete only few cytokines. The pro-inflammatory microenvironment induced by the tumour cells forwards the recruitment and differentiation of macrophages and moreover the activation of local endothelial cells. This step promotes metastasis by breast cancer cells and might offer an interesting new approach for developing targeted therapies.

6

PROGNOSIS AND SURVIVAL OF MEN WITH METASTATIC BREAST CANCER

R. Foerster, F. Foerster, C. Rudlowski, V. Wulff, J.-O. Habeck, B. Schubotz, R. Lange and D. Baaske

Petrzilkova 2583/15, 15800 Praha 5, Czech Republic

Introduction: Only about 1% of breast cancers occur in men, respectively 400-500 new cases per year in Germany. Clinical studies on breast cancer in men are limited for case studies or retrospective analysis. In the recent years no studies have been published on the clinical course of metastatic breast cancer in men. Therefore a retrospective cohort study on this topic is hereby presented. *Patients and Methods:* Clinical and pathological tumor characteristics and the follow-up of male breast cancer patients with metastatic disease diagnosed in the region of Chemnitz/Zwickau in the state of Saxony between 1995 and 2007 were documented and statistically evaluated. *Results:* Thirty five men were diagnosed with metastatic breast cancer; 10 (28.6%) of them with primary metastasis. The median survival time was 37 months. The most common localizations of the metastasis were bones (n=19), lungs (n=19) and liver (n=7). If a systemic therapy was given the prognosis was significantly improved ($p<.005$). The therapy in the metastatic state was very heterogeneous and consisted of systemic endocrine therapy and/or systemic chemotherapy. In 14 (40%) cases a palliative radiotherapy was administered. The initial tumor characteristics like tumor size, nodal state and grading were not of any prognostic relevance on a future development of metastasis. Prognostic unfortunate were a negative hormone receptor state ($p<.001$) and triple negative receptor state (n.s.). Patients with primary metastasis showed a tendency towards worse survival than patients who developed the metastasis during follow-up (n.s.). *Discussion:* Patients suffering from metastatic male breast cancer had a comparatively good prognosis and showed a significant benefit from systemic therapy in this study. In patients with negative receptor state and without systemic therapy the prognosis was especially worsened. The data suggest that an up-to-date adequate systemic therapy is capable of improving survival in men with metastatic breast cancer.

7

FREQUENCY OF NEURAL LESIONS IN ENDOSCOPIC OPERATIONS: RESULTS OF A RETROSPECTIVE MULTI-CENTER STUDY WITH 293,028 LAPAROSCOPIC OPERATIONS

N. Gehrmann, K. Kolmorgen, H.H. Riedel, C. Fotopoulou, W. Lichtenegger and J. Sehouli

Charité, Campus Rudolf-Virchow, Augustenburger Platz 1, 13353 Berlin, Germany

Study Objective: The objective of the study was to examine the frequency of neural lesions in gynaecologic endoscopic operations. Furthermore, the underlying causes of the injury, therapeutic intervention and the clinical outcome were also evaluated. *Design:* The present study presents data regarding the frequency of neural lesions in laparoscopic/pelviscopic surgery in clinics. The statistics encompass collected data of 293,028 laparoscopic operations from 360 hospitals over a three-year period. The analyses based on a questionnaire including x questions. *Measurements and Main Results:* Altogether 94 patients suffered from nerve complications, 37 lesions occurred on the N. cutaneus femoralis lateralis, 24 lesions occurred on other nerves not further specified and in 12 lesions of the N. peroneus were observed. Seven lesions occurred on the genitofemoralis and Plexus brachialis, 3 lesions on the N. obturatorius and 2 lesions each on the N. femoralis and the N. ischiadicus. Lesions occurred due to inadequate bearing surgery (47.8%), mechanical laproscopic instruments (44.7%) and 7.4% of the nerve complications were due to electrosurgical instruments. Fifty one lesions were managed conservatively (through drug therapy or physiotherapy), 7 lesions required surgical intervention. *Conclusion:* Neural lesions are very rare complications of endoscopic surgeries with an excellent long-term prognosis. An improvement in the intraoperative positioning of the patient could potentially improve the incidence of the neural injuries. Therefore systematic educational programmes for the whole medical staff should be conducted.

8

THE SUCCESS-TRIAL – TOXICITY ANALYSIS OF A PHASE III STUDY EVALUATING THE ROLE OF DOCETAXEL AND GEMCITABINE IN THE ADJUVANT THERAPY OF BREAST CANCER PATIENTS

E. Genss[1], H. Sommer[1], J. Sehouli[2], W. Lichtenegger[2], A. Schneider[3], M.W. Beckmann[4] and K. Friese[1]

[1]Frauenklinik der LMU München;
[2]Frauenklinik der Universität Charité Berlin Campus Virchow;
[3]Frauenklinik der Universität Charité Berlin Campus Benjamin Franklin;
[4]Frauenklinik, Universitätsklinikum Erlangen, Germany

Background: In several randomized trials, taxane containing regimens have demonstrated superiority compared to mere anthracycline containing schedules for the adjuvant treatment of patients with early breast cancer. Given an array of novel drugs, continued improvements in the adjuvant setting may further reduce breast cancer mortality in the future. *Methods:* The SUCCESS-Study is an open-label randomized controlled, Phase III study comparing the disease free survival after randomisation in patients treated with 3 cycles of Epirubicin (100 mg/m^2)-Fluorouracil (500)-Cyclophosphamide (500, FEC)-chemotherapy followed by 3 cycles of Docetaxel (100 mg/mg^2, D) *versus* 3 cycles of FEC followed by 3 cycles of Gemcitabine (1,000 mg/m^2 d1,8)-Docetaxel (75 mg/m^2) (DG). Complete, monitored toxicity data of 2.691 patients were available for this analysis. *Results:* Cytostatic treatment was prematurely stopped in 119 patients (4,4%) receiving FEC-DG and in 103 patients (3.8%) with FEC-D (p=0.21). Dose reduction >20% (3.97% *vs*. 2.90%) and postponement of treatment cycles >7 days (22.85% *vs*. 14.19%) was rare, but more frequent in the FEC-DG arm (both p<0.001). G-CSF support was applied in 850 (29.2%) *vs*. 602 patients (20.7%, p<0.001). Toxicities NCI grade >2 which occurred with incidence >1% or significantly different in the two arms are depicted in Table I. Afebrile and febrile neutropenia and anemia did not differ between the two arms, but thrombocytopenia was more frequent in FEC-DG (1.7%, p=0.007). Hand-foot syndrome and neuropathy was more frequent in the FEC-D arm (p=0.09 and p=0.02, respectively). *Conclusion:* Severe adverse effects were rare in both treatment arms. The addition of gemcitabine to FEC-D adjuvant chemotherapy increases toxicity moderately. These findings will have to be interpreted in the context of survival outcome results.

9

EXPRESSION OF FOS-TRANSCRIPTION FACTORS IN EPITHELIAL OVARIAN CARCINOMA

Sibyll Hein, Christine Baasch, Sven Mahner, Fritz Jänicke and Karin Milde-Langosch

Klinik für Gynäkologie, UKE Hamburg, Martinistraße 52, 20251 Hamburg, Germany

Introduction: Members of the Fos protein family dimerise with Jun proteins to form the AP-1 transcription factor complex (Activating-protein 1). They play a central role in proliferation and differentiation of normal tissue as well as in oncogenic transformation and tumor progression. The expression of c-

Table I.

Toxicity	FEC-DG	FEC-D	Percentage		*p*-value
	Grad > 2	Grad > 2	FEC-DG	FEC-D	
Neutropenia	504	508	0.3490	0.3458	0.9984
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0×10^9/L, fever >=38.5 degrees C)	42	59	0.0291	0.0402	0.4454
Anemia	31	20	0.0215	0.0136	0.4556
Thrombocytopenia	25	6	0.0173	0.0041	0.0070
SGPT (ALT) (serum glutamic pyruvic transaminase) elevation	68	28	0.0471	0.0191	0.0004
GGT (Gamma-Glutamyl transpeptidase)	45	34	0.0312	0.0231	0.6205
Vomiting	55	58	0.0381	0.0395	0.9981
Nausea	43	45	0.0298	0.0306	0.9994
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	24	26	0.0166	0.0177	0.9971
Diarrhea patients without colostomy	41	39	0.0284	0.0265	0.9927
Fatigue (lethargy, malaise, asthenia)	40	46	0.0277	0.0313	0.9539
Bone pain	28	44	0.0194	0.0300	0.3381
Thrombosis/embolism	28	22	0.0194	0.0150	0.8396
Arthralgia (joint pain)	24	29	0.0166	0.0197	0.9409
Headache	21	10	0.0145	0.0068	0.2469
Myalgia	20	37	0.0139	0.0252	0.1809
Dyspnea	19	24	0.0132	0.0163	0.9175
Hand-foot skin reaction	15	33	0.0104	0.0225	0.0876
Neuropathy	9	28	0.0062	0.0191	0.0227

Fos, FosB, FosB2, Fra-1 und Fra-2 were analysed to investigate the function of Fos transcription factors in ovarian cancer. *Methods:* Tissue from patients with ovarian cancer (benign tumors, LMP tumors, metastases and invasive carcinomas) was snap frozen after surgery and the expression of c-Fos, FosB/FosB2, Fra-1 and Fra-2 proteins was analyzed by Western Blots and quantified by densitometry. For statistical analysis, the cases were divided into equal groups representing low, moderate and high expression of the analysed transcription factor. These groups were compared with respect of established clinical and biological parameters and survival data. *Results:* The expression of Fra-2 was increased in invasive carcinomas in comparison to benign ovarian tumors. Otherwise, the expression of c-Fos and FosB in metastases was considerably lower than in primary tumors. In a cohort of 101 invasive carcinomas, a moderate or high c-Fos expression was significantly associated with an extended overall survival (median overall survival: 23.8; 46.0 and 55.5 months for low, moderate and high expression, p=0.003). In addition, high c-Fos expression was associated with significantly longer progression-free survival (26.0, 31.6 and 51.2 months for low, moderate and high expression, p=0.003). The expression of the Fos proteins FosB, FosB2, Fra-1 and Fra-2 did not show a significant correlation to established prognostic factors and to course of disease. *Conclusion:* A prior analysis of an independent collective could demonstrate a decreased c-Fos expression in G2/G3 ovarian cancer in comparison to borderline and G1 carcinomas. In this study, it is demonstrated for the first time that loss of c-Fos expression correlates with disease progression and that c-Fos might be an independent prognostic factor in ovarian cancer.

10
SIMULTANEOUS STUDY OF DOCETAXEL BASED ANTHRACYCLINE FREE ADJUVANT TREATMENT EVALUATION, AS WELL AS LIFESTYLE INTERVENTION STRATEGIES SUCCESS C-STUDIE

P. Hepp[1], H. Sommer[2], M.W. Beckmann[3], W. Lichtenegger[4], H. Hauner[5], A. Schneeweiss[6], D. Chatsiproios[7], B. Rack[2], E. Genss[2], J. Jückstock[2] and W. Janni[1]

[1]Frauenklinik der Universität Düsseldorf;
[2]Frauenklink der Universität München;
[3]Frauenklinik der Universität Erlangen;

[4]Frauenklinik der Charité Berlin Campus Virchow;
[5]Else-Kröner-Fresenius-Zentrum für Ernährungsmedizin der TU München;
[6]Frauenklinik der Universität Heidelberg;
[7]Gynäkologische Gemeinschaftspraxis Mannheim, Germany

Background: Taxane based chemotherapy, like the PACS 01 regimen (3xFEC100, followed by 3xDocetaxel100) has been established as the standard treatment option for early breast cancer; Anthracycline-based regimens do not seem to be superior in HER2-negative patients. Dietary intervention seems to improve the outcome in patients with early breast cancer. The prognostic relevance of isolated tumor cells in bone marrow has recently been proven and early data indicates a prognostic relevance of circulating tumor cells in peripheral blood. *Methods:* The SUCCESS-C Trial is a prospectively randomized multicenter clinical trial for early, HER2/neu-negative breast cancer patients. The study comprises two sequential randomizations. The first randomization of the study compares the disease-free survival in patients treated with 3 cycles of Epirubicin (100 mg/m^2)-Fluorouracil (500)-Cyclophosphamide (500, FEC)-chemotherapy, followed by 3 cycles of Docetaxel (100 mg/mg^2, D) *versus* 6 cycles of Cyclophosphamide (500 mg/m^2 q3w)-Docetaxel (75 mg/m^2) (DC). The second randomization examines the benefits of standardized lifestyle dietary intervention and weight reduction, conducted by intensive telephone coaching. The telephone intervention involves 19 phone calls, as well as mailings and a participant manual. Women in the interventional group are asked to lose up to 10% of their weight by reducing their caloric and fat intake and increasing their physical activity moderately. Adjunct to these interventional strategies is a translational research program, which focuses on the role of CTCs as valuable marker of treatment failure and early disease progression. At three predefined time points during treatment peripheral blood is drawn. *Results:* Results of the toxicity analysis and the translational research program will be available at the end of treatment. First conclusions about the effects on DFS are expected two years after the end of chemotherapeutic treatment or lifestyle intervention, respectively.

11
ULTRASOUND EXAMINATION OF THE BREAST FOR EVALUATION OF RESPONSE DURING PRIMARY SYSTEMIC THERAPY OF BREAST CANCER

Ines Koch, Anne Egbe, Scarlett Lejavova, Oumar Camara and Ingo B. Runnebaum

Department of Gynaecology, Interdisciplinary Center for Breast Diseases, University Hospital Jena, Germany

Introduction: The number of breast cancer patients undergoing neoadjuvant therapy is constantly growing. During this therapy palpation, mammography, ultrasound of the breast and MRI are used for evaluation of therapy results. Ultrasound of the breast is very common and a valuable method for prompt information about response to primary chemotherapy. The aim of this investigation is to compare routine ultrasound monitoring to mammography and MRI-evaluation at the beginning and at the end of primary chemotherapy. *Method:* From 2002 to 2008 128 patients with breast cancer in stadium cT2-4 who underwent a primary systemic therapy were prospectively evaluated. Before every cycle of chemotherapy, an ultrasound examination of the breast took place. Furthermore, in every case a mammography was performed at the beginning and at the end of chemotherapy. Since July 2002, a MRI of the breast was added. Finally, differentiation was made on ultrasound, mammography and MRI findings between stable disease (SD), progressive disease (PD), partial remission (PR, tumor reduction ≥50%) or complete remission (CR, included DCIS). The clinical remission was compared to histopathology results after operation. *Results and Discussion:* From 125 patients undergoing operation a complete remission was histopathologically diagnosed in 22.4% . After chemotherapy, ultrasound discovered these cases in 48.1% , mammography in 28.6% and MRI in 27.3% . Partial remission and stable disease were correctly diagnosed with ultrasound in 88.1% and 40.0% , with mammography in 59.2% and 62.5% and with breast MRI in 90.6% and 41.2% . Progression was safely detected with all examination methods. Ultrasound is able to provide highly qualitative and valid results despite of variance of measuring. With constant availability and a high cost effectivness ultrasound of the breast seems to be a favourable option as compared to palpation. Mammography alone seems to be inadequate to specify the extent of breast cancer after primary chemotherapy. MRI appears to detect partial remission and stable disease more reliably. For planning operation, mammography and breast MRI should be used in addition to ultrasound.

12
EVIDENCE-BASED PSYCHOONCOLOGICAL CARE FOR BREAST CANCER PATIENTS

M. Kusch, C. Kost, C. Herrmann-Lingen, C. Wagner and H. Labouvie

Institut für Gesundheitsförderung und Versorgungsforschung gGmbH, Bochum, Germany

The best available evidence for effective and efficient psychooncological care in routine health care practice has been formulated by the Institute of Medicine in 2008 within a model for the effective delivery of psychosocial health

services. Key recommendations of this model include the identification of psychosocial health needs, the coordination of psychosocial and biomedical health care, and the follow-up on care delivery to monitor the effectiveness of services. These aspects have been the basis of the structured psychooncological care program "Case Management Psychooncology" (CMP) and the project "implementation of psychooncological health services in hospitals" in North Rhine Westphalia (NRW; Germany). The program has been implemented in six hospitals. The partners of the project were the Health Ministry of NRW, the health insurance company AOK-WL and the Hospital Society of NRW (KGNW). *Methods:* The structured psychooncological care was carried out using intranet available clinical pathways, standard operating procedures separated for each profession and an MS-Access-based documentation system. Instruments were the „Hospital Anxiety and Depression Scale" (HADS) and a checklist assessing the patients psychosocial needs. *Results:* Between 2004 and 2006 psychooncological interventions were carried out with a total of 5,443 cancer patients, of which 930 had breast cancer. Based on the HADS total cut-off score of >14, the need for psychooncological care at hospital admission was indicated for 50.7% of breast cancer patients. The average duration of care was 7 months, the average frequency of care was 5.5 consultations and the average intensity of care was 3.8 hours. Clinically significant improvements of anxiety and depression could be identified in 35.4% of the breast cancer patients with high distress (HADS cut-off score >14) 138 days after hospital admission and in 47.6% of the cases one year after hospital admission. *Conclusion:* The results demonstrate that a structured psychooncological care program can be implemented in clinical practice as recommended.

13

PREFERENCE FOR ORAL OR INTRAVENOUS TREOSULFAN IN ELDERLY-PATIENTS WITH RECURRENT OVARIAN CANCER – PLANNED INTERIM SAFETY ANALYSIS OF A PROSPECTIVE MULTICENTER-STUDY

Sven Mahner, Gülten Oskay-Oezcelik, Elke Heidrich-Lorsbach, Lothar Müller, Stefan Fuxius, Harald Sommer, Peter Klare, Antje Belau, Dieter Ullrich, Thomas Heuser, Fritz Jänicke, Werner Lichtenegger and Jalid Sehouli

North-Eastern German Society of Gynaecological Oncology (NOGGO)

Background: Treosulfan is an alkylating agent that has demonstrated activity in recurrent ovarian carcinoma. It is effective as oral (PO, 97% bioavailability) and intravenous (IV) formulation. Primary aim of this study was to explore the preference and compliance of elderly patients (age 65 and above) for PO or IV-treosulfan for the treatment of relapsed ovarian carcinoma. Secondary aims were to evaluate toxicity, response and survival as well as geriatric assessment. *Methods:* Patients had a free choice of treosulfan-IV (7 g/sq day 1 of a 28-day cycle) or PO (600 mg/sq day 1-28 of a 56-day cycle) until disease-progression. Indecisive patients were randomized. Compliance was measured by patient-requested therapy-discontinuation. A planned interim safety-analysis was performed after 25 of 100 patients. *Results:* Twenty five of 51 recruited patients completed therapy at the time of the interim analysis (median age 75 years, range 70-82 years), 20 (87%, 95% CI: 66.4 - 97.2%) chose IV and 3 chose PO (p=0.00003), 2 were randomized to IV. Median ECOG performance status was 1 (range 0-2), and the median number of prior chemotherapy-regimens was 2 (range 1-6). A median number of 3 (min 1, max 10) cycles was administered per patient. Grade 3-4 leukopenia was 13.6% (3 of 22 patients) in IV and 0% in PO. Patients with preference for IV stated that they already took a large number of tablets for concomitant morbidities and that their daily life was less affected by monthly infusions. *Conclusion:* Fourty-two of 51 patients (20 of 23 with completed therapy) preferred IV-treosulfan. Both applications were well tolerated and the clinical outcome seems to be comparable to other palliative chemotherapy-regimens for relapsed ovarian cancer.

14

CHANGES OF VEGF AND CAIX SERUM CONCENTRATIONS DURING FIRST-LINE THERAPY OF OVARIAN CANCER PATIENTS

Sven Mahner, Linn Woelber, Joerg Schwarz, Walter Carney, Fritz Jaenicke, Karin Milde-Langosch and Volkmar Mueller

Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany

Background: Angiogenesis appears to play an important role in ovarian cancer. Vascular endothelial growth factor (VEGF) is a direct angiogenic molecule stimulating tumor neovascularization and has recently been implicated as a therapeutic target in ovarian cancer. The role of the cell membrane protein carbonic anhydrase 9 (CAIX) is not yet determined in ovarian cancer. It is induced by hypoxia in certain tumors and has been associated with poor prognosis in renal cell cancer and other solid tumors. The aim of this study was to evaluate the potential role of serum VEGF and CAIX to monitor primary therapy and predict response and clinical outcome of patients with ovarian cancer. *Methods:* Patients with epithelial ovarian cancer who presented for primary surgery were included in this study. A total of 148

serum samples from 37 patients were analyzed. Samples were prospectively collected at 4 predefined time points: 1. before radical debulking surgery, 2. after surgery and before platinum/taxane based chemotherapy, 3. during chemotherapy, 4. after chemotherapy. Serum VEGF-165 and CAIX were quantified by ELISA (Siemens Medical Solutions Diagnostics, Tarrytown, USA) and correlation with response and clinical outcome was analyzed. *Results:* High serum concentration (above median) of CAIX before surgery (p=0.035), VEGF after surgery (p=0.043) and VEGF after chemotherapy (p=0.006) were significantly associated with poor progression free survival while high VEGF serum concentration after chemotherapy (p=0.023) predicted reduced overall survival. A longitudinal decrease of VEGF during therapy was associated with improved progression free (p=0.018) and overall survival (p<0.001). *Conclusion:* VEGF and CAIX serum levels changed substantially during first line therapy of ovarian cancer patients and could predict response and outcome. Findings support the rationale of antiangiogenic therapy in ovarian cancer and suggest a potential role of VEGF and CAIX to monitor response to first line therapy. To further understand the role of these markers, an evaluation in the context of prospective clinical trials is highly desirable.

15

SEQUENTIAL THERAPY WITH CARBOPLATIN (C) FOLLOWED BY PACLITAXEL (P) AS FIRST-LINE CHEMOTHERAPY IN 105 PATIENTS WITH ADVANCED OVARIAN CANCER (AOC): RESULTS OF A MULTICENTER PHASE II STUDY OF THE NORTHEASTERN GERMAN SOCIETY OF GYNECOLOGICAL ONCOLOGY

G. Oskay-Özcelik, R. Chekerov, J. Pfisterer, H. Sommer, E. Keil, J. Einenkel, O. Camara and W. Lichtenegger and J. Sehouli

Department of Gynecology and Obstetrics, Division of Gynecologic-Oncology, Charité-Campus Virchow Klinikum, University Medicine of Berlin, 13353 Berlin, Germany

Background: For the adjuvant setting of AOC after primary radical surgery the combination of paclitaxel and platinum in a three weeks schedule has emerged as the current standard. In animal models additional anti-angionetic effects of low dose paclitaxel infusion was observed. A sequential schedule of these agents can potentially yield an improved therapeutic index. *Methods:* In this multicenter-phase II trial after primary radical surgery 4 cycles of Carboplatin at a dose of AUC 5 (d1/q21d) followed by 12 cycles weekly paclitaxel at a dose of 80 mg/m^2 (d1/q7d) was applied. All patients with haemoglobin levels <12 mg/dl received primary erythropoietin. *Results:* Between 07/2003 and 05/2005, 105 patients from 27 institutions were enrolled. Overall 1457 cycles were applied (median 16 courses / range 0-16). The median age was 60 years (23-80). The incidence of non-hematological and hematological toxicities was very low. Grade 3-4 hematological toxicity (% of all pts) included: thrombocytopenia (16 %), anemia (3%), leucopenia (22%), neutropenic fever (0%). 96% received erythropoietin. Thromboembolic events (5 pat.) were not increased in patients who received erythropoietin. After a median follow-up interval of 25months (range: 1-42 months) the progression free survival was 25.4 months (95% CI: 18.8 - >40 months) and the median overall survival was not reached. *Conclusion:* These results suggest that this sequential regimen using weekly paclitaxel represents an efficacious and well-tolerated regimen. A randomized study comparing this new schedule with the conventional 3-week protocol is warranted.

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16

WHAT DO OVARIAN CANCER PATIENTS EXPECT FROM THEIR CANCER CARE? FINAL RESULTS OF A GERMAN SURVEY OF THE NOGGO AND AGO IN 1060 PATIENTS

Guelten Oskay-Oezcelik, Andreas du Bois, Peter Andreas Fasching , Sven Mahner Clemens Liebrich, Anja Glaß, Sabine Schmidt- Wetzel, Leodolter Sepp, Karsten Muenstedt, Peter Breitbach, Werner Lichtenegger, Jacobus Pfisterer and Jalid Sehouli

Department of Gynecology and Obstetrics, Division of Gynecologic-Oncology, Charité-Campus Virchow Klinikum, University Medicine of Berlin, 13353 Berlin, Germany

Introduction: National and international guidelines recommend routine cancer care for patients with ovarian cancer. Nevertheless only limited data exist about the expectations and information needs of patients from follow-up management. Therefore we initiated a multi-institutional survey. *Methods:* A semi-structured questionnaire consisting of 15 questions was developed in a pilot-study of 20 patients. After this validation all gynaecological departments and gynaecological-oncological practices were invited to participate in this trial using an anonymous print version of the questionnaire. *Results:* Overall 3850 questionnaires were send to 170 institutions. Between October 2006 and April 2008 a total of 1060 patients were enrolled. The median age of the patients was 58 years (range 16-87). 589 patients, who were not in therapy during the survey, were analysed. Patients were informed about the procedures and goals of cancer care predominantly after primary surgery (54%) and in 18% after last cycle of first-line chemotherapy. 8%

declared that they were informed only at the first follow-up visit, 10 % stated that they have never received any information about their cancer care management. CA-125 measurement was the most important procedure for the patient (61%) but with highest anxiety (19%). The main objective for the follow-up was the early detection of relapse and a prolongation of overall survival (84%). Most patients demanded from their physician more time for explanation and treatment options to improve their immunosystem. Finally, most patients (84%) were satisfied from their management of cancer care. *Conclusion:* The present study provides important data for physician-patient communication for follow-up management.

17
THE COMPLEX DIAGNOSIS OF CERVICAL INTRAEPITHELIAL NEOPLASIA

D. Muresan[1], I. Rotar[1], R. Popp[1], S. Apostol[1], G. Coroiu[2], G. Caracostea[1], D. Ona[1] and F. Stamatian[1]

[1]First Clinic of Obstetrics and Gynecology, Univeristy of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca; [2]Infectious Disease Hospital, Cluj Napoca, Romania

The complex diagnosis of the cervical intraepithelial neoplasia requires, nowadays, methods in the field of cytology, colposcopy, molecular diagnosis and pathology in order to get a fine diagnosis and an accurate prognosis. The progress achieved in the ethiopathology of cervical cancer has brought new data which have to be integrated carefully. The aim of this study was the analysis of actual diagnostic methods upon 50 patients that were admitted into the Clinic of Obstetrics and Gynecology, Napoca, Romania diagnosed with intraepithelial neoplasia between 1st of January 2008 and 31 of July 2008. For each patient monolayer cytology and colposcopy were performed. HPV 16 and 18 detection were performed immunohistochemistry using a HPV high risk kit and nested PCR. Biopsies were examined in a pathology laboratory. The maximum concordance between cytology, colposcopy and biopsy appeared in cases of low grade squamous intraepithelial lesion and cervical intraepithelial neoplasia and a discrepancy was found in cases of ASC-H and CIN III. The molecular methods have their particularities related to the stage of the viral infection that needs to be taken into consideration.

18
BRAIN METASTASES IN OVARIAN CANCER: OVERVIEW AND OPTIMAL TREATMENT

Klaus Pietzner, Khalid El Khalfaoui, Gülten Oskay-Özcelik, Dirk Boehmer, Werner Lichtenegger and Jalid Sehouli

Department of Gynecology and Obstetrics, Division of Gynecologic-Oncology, Charité-Campus Virchow Klinikum, University Medicine of Berlin, 13353 Berlin, Germany

Ovarian cancer is one of the leading causes of mortality in the field of gynecologic oncology. Central nervous system (CNS) involvement, however, is rare in presentation and seems to be associated with a very poor prognosis. Clinical as well as autopsy studies in the last decades have confirmed the rarity of occurrence of brain metastases in ovarian cancer, but several authors have recently observed a sharp rise in incidence. While most authors attribute this increase of CNS involvement to prolonged survival achieved through advances in chemotherapy and surgical management, others see it resulting from improved imaging or chemotherapeutic impairment of the blood-brain barrier. Brain metastases from ovarian cancer can present with a panel of often unspecific symptoms which usually results in a late diagnosis of CNS relapse, since cerebral imaging is not part of the routine follow-up. Even serum CA-125 levels, a valuable tool in predicting recurrence of distant disease, was shown to be incapable of reliable detection in regard to metastatic brain manifestation, leaving the clinician with the need for close patient observation for neurological symptoms in order to diagnose brain metastasis at an early stage. While some reports only indicate the presence of extracranial disease at CNS relapse and time from diagnosis of ovarian cancer to development of brain metastases as prognostic factors for survival, other studies demonstrate the negative impact of multiple cerebral lesions on survival, when compared to single brain metastases. Though great efforts have been made to develop multimodal therapeutic strategies to challenge the rising incidence of brain metastasis in ovarian cancer, CNS involvement is still related with a very poor prognosis. It was shown that a multi-modal approach, combining surgical resection with radiation therapy and even chemotherapy promises the best prolongation of survival and did result in long-term remissions in a few cases. But this aggressive strategy is not applicable to all patients, often due to overall status or inaccessibility of brain metastases to the neurosurgical approach. In these cases stereotactic radiation therapy or gamma-knife-surgery is recommended by many authors to remove single metastatic brain lesions. These techniques should be further discussed as an alternative for whole-brain radiation therapy, as several studies expand its use to other indications such as multiple lesions and with promising results. Based on a large multicenter study including 73 patients with brain metastases from ovarian cancer, predictive and prognostic factors as well the current best treatment will be discussed in this paper.

19

TUMOR BANK OVARIAN CANCER (TOC) – NETWORK A PROSPECTIVE MULTICENTRIC PROJECT FOR APPLIED CLINICAL RESEARCH AND INTERDISCIPLINARY COOPERATION

J. Sehouli[1], D. Könsgen[2], R. Chekerov[1], P. Altevogt[3], E. Dahl[4], C. Denkert[5], M. Dietel[5], G. Köhler[2], S. Leodolter[6], S. Olek[8], P. Nürnberg[9], A. Rosenthal[10], D. Sofroni[7], E. Stickeler[11], A.H. Tulusan[12], R. Zeillinger[6] and W. Lichtenegger[1]

[1]Charité, Department of Gynecology, University of Berlin;
[2]Ernst-Moritz-Arndt-University, Department of Gynecology, Greifswald;
[3]Deutsches Krebsforschungszentrum, Heidelberg;
[4]University Aachen, Institute for Pathology;
[5]Charité, Institute for Pathology, University of Berlin, Germany;
[6]Medical University of Vienna, Department of Obstetrics and Gynecology, Austria;
[7]Institute for Oncology Chisinau, Department of Gynecology;
[8]Epiontis, Berlin;
[9]Cologne Center for Genomics, University of Cologne;
[10]Signature Diagnostics, Potsdam;
[11]Albert-Ludwig-University, Department of Gynecology, Freiburg;
[12]Clinical Center Bayreuth, Department of Gynecology, Germany

The Tumor Bank Ovarian Cancer (TOC) project was started in September 2000 in the Charité, Campus Virchow, Department of Gynecology and Obstetrics. Between September 2000 and July 2004, overall 420 patients with primary and recurrent ovarian cancer were prospectively documented and recruited into TOC. Tumor, ascites, serum and blood were collected from each patient after having given their informed consent. The tumors were collected at the time of surgery, shock-frozen and stored at –180˚C in a Dewar Tank containing liquid nitrogen, the blood and ascites specimens at –80˚C. In median, 10 (range 1-25) samples were available from each donor. The following specimen requirements were defined: Each tumor was classified by the Pathology department upon resection, and anonymous basic data about each tumor was kept in the database with all relevant clinical, histo-pathological and follow-up data. Furthermore, a systematic surgical and histo-pathological tumor documentation system (Intraoperative Mapping of Ovarian Cancer - IMO) was developed and validated. IMO represents a new instrument for detailed and objective documentation of tumor spread and helps hereby to provide a more specific tumor staging. This prospective documentation represents a valid instrument for standard operating procedures and quality control. On January 2004 the project TOC-Network was initiated, a tumor bank with a multi-centric setting. Overall, seven European Hospitals are involved in this project. Each university hospital uses the same SOP's and online documentation tool. For the statistical analysis an online documentation tool was developed in which all clinical, surgical and follow-up data from all patients with ovarian cancer are registered. Since January 2004 1078 patients have been enrolled into TOC Network. The prospective tumor bank allows to assess and verify the clinical relevance of basic science of ovarian cancer and provides an essential link between basic research and applied clinical research. Based on the experience the logistic and the established infrastructure will be used for further clinical and preclinical projects. The scientific board of TOC is very open to all suggestions for collaborative research projects.

20

PRIMARY BREAST CANCER CELLS AND THEIR METASTASES SHOWED SIGNIFICANT DIFFERENCES OF EXPRESSION OF CATHEPSIN-D, WHICH IS INVOLVED IN ADHESION OF BREAST CANCER CELLS

Naim Shabani[2], Ioannis Mylonas[1], Christina Kuhn[1], Christiane Kunert-Keil[3], Christian Schindlbeck[1], Bernd Gerber[4], Oumar Camara[2], Ingo B. Runnebaum[2], Klaus Friese[1] and Udo Jeschke[1]

[1]Department of Gynecology, and Obstetrics, Ludwig-Maximilians-University of Munich, 80337 Munich;
[2]Department of Gynecology and Obstetrics, Friedrich Schiller University Jena, 07743 Jena;
[3]Ernst Moritz Arndt University of Greifswald, Institute of Pathophysiology, 17459 Karlsburg;
[4]Department of Gynecology and Obstetrics, University of Rostock, Germany

Specific objectives: Breast cancer cells can invade and generate metastasis *via* either lymphatic or blood vessels. A critical factor for metastasis is cathepsin-D, a lysosomal protease. Cathepsin-D increases the incidence of metastasis and is involved in cell proliferation and inhibition of tumor cell adhesion. In this study the expression of cathepsin-D has been analysed in mammary carcinoma *in situ*, invasive breast carcinomas without metastasis, invasive carcinomas with their lymph node and distant metastasis and invasive carcinomas with local recurrence in breast cancer tissue. *Methods:* A total of 37 paraffin embedded slides of carcinoma *in situ* (DCIS, n=8), invasive carcinomas without lymph node metastases (n=9), invasive carcinomas

with corresponding lymph node metastases (n=7), invasive carcinomas with corresponding recurrence (n=5) and invasive carcinomas with corresponding distant metastases (n=5) were investigated for cathepsin-D expression. For immunohistochemistry staining mouse IgG antibody (1 µg/ml, Dianova, Hamburg, Germany) was used. *Results:* A strong expression of cathepsin-D in carcinoma *in situ* was demonstrated. Expression of cathepsin-D was moderate in invasive carcinomas without metastases and in invasive carcinomas with corresponding lymph node metastases. Cathepsin-D expression was reduced in lymph node metastases compared to the primary tumor, in primary tumors with recurrence, in recurrence tissue and in primary tumors with distant body metastases and in its metastases. *Conclusion:* Analysis of cathepsin-D which is involved in adhesion of breast cancer cells showed that there are significant differences of expression of cathepsin-D in primary breast cancer cells and their metastases. Evaluation of this marker could be a useful method for evaluating the metastatic risk in breast cancer patients.

21

PREDICTION OF INTESTINAL TUMOUR INVOLVEMENT BY PARAMETERS OF NUTRITIONAL STATUS IN PATIENTS WITH PRIMARY OR RECURRENT OVARIAN CANCER

Paulina Skowronek, Marc Kuhberg, Frank K. Chen, Dominique Koensgen-Mustea, Werner Lichtenegger and Jalid Sehouli

Department of Gynecology and Obstetrics, Charité University Medicine Berlin, Campus Virchow-Klinikum, Berlin, Germany

Introduction: Global malnutrition is widespread among patients with ovarian cancer. Therefore, the objective of this prospective study is to investigate the influence of tumour localisation and stage on nutritional status of patients with ovarian cancer. *Materials and Methods:* In a one-year-period (April 2007 - March 2008) 75 patients were documented, 29 (39%) of them had primary and 46 (61%) recurrent disease. At the time of admission for surgical therapy, the body composition was analysed with Bioelectrical Impedance Analysis (BIA) using phase angle α and ratio of Extra-Cellular Mass and Body Cell Mass (ECM/BCM). Additionally, basic anthropometric data and serum protein parameters were registered. The risk of malnutrition was estimated by Nutritional Risk Score (NRS-2002). During operation a standardised documentation script (IMO) was performed including tumour localization, intestinal involvement and surgical interventions. Nutritional parameters were correlated with IMO-parameters. *Results:* The median age of patients was 57 years (49-66) with median BMI 24.6 kg/m^2. In 21% primary and 15% recurrent cases high nutritional risk was documented (NRS≥3). These patients had significantly lower serum albumin, pre-albumin and transferrin levels compared to patients with NRS<3 (p<0.05). FIGO stage correlated negatively with phase angle α and positively with ECM/BCM in patients with primary diagnosis. In patients with primary or recurrent disease who needed surgical resection of small or large intestine, phase angle α and serum albumin level were significantly lower than in patients with no intestinal involvement (p<0.05). *Conclusion:* Independent on tumour stage, preoperative evaluation of nutritional status with BIA, especially phase angle α, is a valid method to predict intestinal tumour involvement in patients with ovarian cancer.

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Authors Index (Figures indicate abstract number)