quantitative RT-PCR was performed to evaluate the relationship between relative mRNA expression and protein expression.
Results:
1. CC had significantly higher levels of ABCF2 expression than other histologic type.
2. Fifty six CC patients received platinum-based chemotherapy after primary debulking surgery and the response to chemotherapy was evaluable in 12 of them.
3. Forty three of 61 (70.5%) patients showed ABCF2 expression and the relative mRNA expression was significantly correlated with levels of ABCF2 protein expression ($r = 0.5$, $p = 0.006$).
4. A clinical response to chemotherapy was obtained in 5 of 12 (42%) cases.
5. Non responders had significantly higher levels of ABCF2 protein expression than responders (59% vs 25%, $p = 0.0007$).
6. The OS was 75% (median follow-up of 36 months). The OS for patients without ABCF2 expression was significantly higher than the OS for patients with ABCF2 expression (94% vs 67%, $p = 0.03$).

Conclusions: The present results indicate that ABCF2 expression may predict the response to chemotherapy and survival of CC patients.

913 POSTER

Plasminogen Activator Inhibitor-1 RNA Binding Protein expression in epithelial ovarian cancer

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Background: The plasminogen activator-plasmin cascade plays a central role in tumor cell invasion and metastasis of solid tumors. The type-1 plasminogen activator inhibitor (PAI-1) is the major physiologic regulator of the plasminogen activation. The novel Plasminogen Activator Inhibitor-1 RNA Binding Protein (PAI-RBP1) is suggested to play a crucial role in cyclic nucleotide-mediated regulation of PAI-1 mRNA stability. The expression of PAI-RBP1 in ovarian cancer is unknown. We are the first working group to analyse the expression of PAI-RBP1 in ovarian cancer.
Methods: Identification of overexpressed genes in ovarian cancer by in-silico analysis (AUTEX, e-NORTHERN, BLAST). In a second step analysis of the expression of PAI-RBP1 by in-situ hybridization was performed. Tissue sections of paraffin-embedded tumor specimens from patients with benign and malignant ovarian tumors, who underwent surgical intervention in the Department of Gynaecology and Obstetrics, Charité, from 02/01 to 06/02, were used. All samples were obtained from Tumor Bank Ovarian Cancer (TOC). Correlation analysis with conventional clinical factors was performed by using SPSS (SPSS Inc., V.11,0; Chicago 2001).
Results: 57 patients (28 primary ovarian cancer, 15 recurrent ovarian cancer, 3 low-malignant potential ovarian tumors, 6 benign ovarian tumors, 5 normal ovary) were allocated to this trial. Median age was 57 years (range, 34–86). Median follow-up was 20 months (range, 0–64). The distribution of tumor stage FIGO of all primary ovarian cancer was: I = 16.2%, II = 3.2%, III = 45.2% and IV = 35.5%. PAI-RBP1 was significantly overexpressed in tumor epithelium of ovarian cancer in comparison to ovarian epithelium of benign ovarian tumors and normal ovary ($p = 0.002$). In statistical analysis a significant correlation between the PAI-RBP1 expression and FIGO-stage was observed ($p = 0.014$).
Conclusions: PAI-RBP1 is significantly overexpressed in OC and correlates with the clinical tumor stage FIGO. The prognostic role of PAI-RBP1 will be analysed after a longer follow-up period.

914 POSTER

Shedding of GPI-anchored proteins from ovarian cancer cells promotes pericellular plasmin generation and cell invasion

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Background: In human ovarian cancer, soluble forms of glycosylphosphatidylinositol (GPI)-anchored proteins (e.g. the protease receptor, urokinase receptor [uPAR], and CA125) accumulate in the ascitic fluid and the blood of the patients, and their concentration has prognostic significance. uPAR regulates cell surface plasmin generation. We have shown previously that GPI-anchored proteins are released from ovarian cancer cells in vitro by GPI anchor hydrolysis catalyzed by cellular GPI-specific phospholipase D (GPI-PLD). Here, we describe the role of this enzymatic event in regulating pericellular proteolysis and ovarian cancer cell invasion.
Materials and methods: Transfections with cDNA constructs and siRNA were performed using Lipofectamine Plus. Stable cDNA transfectants were isolated by G418 selection and cloned by limiting dilution. Plasmin generation was determined using the chromogenic substrate, S-2251. Cell invasion was measured using a double-filter assay and fibrin or the basement membrane extract, matrigel, as substrates.
Results: By targeting GPI-PLD expression in human OV-MZ-13 ovarian cancer cells using stable antisense cDNA transfection, uPAR shedding was reduced up to 4-fold in selected antisense clones as compared to control clones. Cell invasion into fibrin (80% inhibition with non-cloned antisense transfectants) or matrigel (93% inhibition with antisense clones), was almost completely abolished by GPI-PLD antisense targeting. Similar inhibitory effects were seen with GPI-PLD-specific siRNAs, which reduced GPI-PLD expression approximately 4-fold. Inhibition of cell invasion by GPI-PLD antisense targeting appeared to be caused by two distinct effects: (i) Reduction in cell surface uPAR expression (45% inhibition) and plasminogen activation (30% inhibition), which was most likely due to the diminished formation of the bioactive GPI anchor cleavage product, phosphatidic acid. Exogenous phosphatidic acid increased uPAR expression 2-fold. (ii) Decrease in extracellular-matrix associated plasmin generation (up to 84% at the conal level) due to reduced uPAR shedding (75% inhibition) and soluble uPAR binding to matrigel (53% inhibition).
Conclusions: Shedding of GPI-anchored proteins enhances cell surface and pericellular proteolysis and is required for ovarian cancer cell invasion. Thus, GPI-PLD is a malignant property of ovarian cancer cells with potential significance as a prognostic marker and/or therapeutic target.

915 POSTER

Paclitaxel/Carboplatin (TC) versus Paclitaxel/Carboplatin followed by Topotecan (TOP) in first line treatment of advanced ovarian cancer. Mature results of a Gynecologic Cancer InterGroup (GCIG) phase III trial of the AGO OVAR and GINECO

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Background: A randomized phase III trial was performed in patients (pts) with advanced ovarian cancer (OC) to determine the role of Top in first line treatment. The sequential manner was chosen to incorporate Top as a non cross resistant third drug to TC by avoiding the toxicity of a simultaneous triple drug regimen.
Material and methods: Between 12/1999 and 03/2002 1,308 pts with previously untreated OC FIGO stages IIB–IV were randomized to receive 6 cycles of Paclitaxel (175 mg/m^2 3h iv) and Carboplatin (AUC 5, Calvert formula) (TC) followed by surveillance or 4 cycles of Topotecan (1.25 mg/m^2 iv d1–5) (Top) on a 3 week schedule. Pts were stratified within each center according to residual tumor size and FIGO stage: stratum 1 "FIGO stage IIB–IIIC and residual tumor $\leqslant$1 cm", and stratum 2 "FIGO stage IIB–IIIC and residual tumor >1 cm or FIGO IV". The primary endpoint was overall survival (OS). This study was designed to show an increase in 3 year survival of 8% with a power of 80% using a stratified log-rank test with alpha set to 5%. To detect this effect at least 541 events were necessary.
Results: 658 pts were assigned TC followed by Top and 650 TC. Overall, 9453 treatment cycles were administered, 5564 in the TC-Top arm and 3889 in the TC arm. During treatment with TC, no relevant difference in Grade (G) 3/4 hematologic and non-hematologic toxicity between both study arms was observed. The median doses of TC were given as scheduled, as were the median intervals between therapy courses. Top myelotoxicity resulted in treatment delays of at least 7 days in 18.4% of Top courses. G 3/4 anemia occurred in 6.4% of all Top courses, thrombocytopenia in 10.7%, leukocytopenia in 28.0% and neutropenia in 57.0%. However, this was of minimal clinical relevance in terms of febrile neutropenia (0.9%) or infections (0.9%) in pts treated with Top. Median Top dose/course/day for all courses was 1.25 mg/m^2. Response data were available from 145 and 147 pts with measurable disease in the TC-Top and TC arm. TC-Top was associated with 69.0% clinically complete and partial responses; TC with 76.2% (ns). 947 of the 1308 pts had progressed and 625 pts had died. PFS for pts with/without Top was 18.2 months vs. 18.5 months, corresponding to an adjusted HR of 0.97 (95%-CI 0.85–1.10, $p = 0.688$). There was also no significant difference in overall survival with a median of 43.1 months in the TC-Top arm and 44.5 months in the TC arm (adjusted HR = 1.01, 95%-CI 0.86–1.18, $p = 0.885$).
Conclusions: The addition of Top to TC did not result in superior OR, PFS and OS. Therefore, TC-Top cannot be recommended as first-line therapy of advanced OC.