Conclusions: Weekly administration of topotecan shows no substantial difference in endpoints of effectiveness compared to conventional dosing, but is associated with a significantly lower likelihood of severe hematological toxicity. Weekly topotecan should be considered as a possible treatment alternative in women with platinum-resistant ovarian cancer.

8003 ORAL

Bevacizumab in heavily pre-treated ovarian cancer patients and the predictive value of serum VEGF

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Background: Ovarian cancer remains the leading cause of death in gynecologic malignancy in the western world and therefore new treatment strategies are urgently needed. Bevacizumab, a recombinant humanized monoclonal antibody against VEGF (Vascular Endothelial Growth Factor), has shown antitumor activity in several cancer types including ovarian cancer with acceptable toxicity. The purpose of the present study was to evaluate treatment with single agent bevacizumab in heavily pre-treated advanced epithelial ovarian cancer patients, expressed by RR (response rate), PFS (progression free survival) and OS (overall survival).
Furthermore we aimed at defining the possible prognostic and predictive value of serum VEGF analyzed in blood samples by each cycle.
Material and Methods: Thirty-eight patients with advanced ovarian cancer were treated with bevacizumab every three weeks, 10 mg/kg. Serum VEGF concentration was analyzed before treatment and in every cycle by ELISA technique (Quantikine ELISA kit no: 1190951, R & D Systems, Minneapolis, USA).
Results: The median number of prior regimens was five and the median number of bevacizumab treatment cycles was four. Thirteen patients were still under treatment at the time of analysis. Nine out of 33 evaluable patients (27%) showed response by CA 125 according to the modified GCIG criteria's. Median PFS was 6.3 months (95% CI; 3.5−17.7) and median OS was 8.2 months (95% CI; 5.0−9.2).
Two patients suffered from gastrointestinal perforation during treatment, one from ileo-vaginal fistula and two were diagnosed with trombo-embolia and transient cerebral ischemia.
All patients decreased their serum VEGF concentration after the first cycle of treatment with a mean of 89%. There was a significant difference in VEGF level between responders and no responders ($p = 0.004$). The CA 125 response rate was 63% for VEGF <275 pg/ml whereas 14% for VEGF > 275 pg/ml ($p = 0.009$). This cut off was chosen as the 25% percentile for all serum VEGF analyses. No association with clinicopathological parameters was demonstrated and no significant difference in PFS or OS was shown according to low/high serum VEGF.
Conclusion: Single agent bevacizumab therapy demonstrated activity in heavily pre-treated ovarian cancer women with a CA 125 response rate of 27%. Gastrointestinal perforations were identified in 5% of patients. Baseline serum VEGF levels seem to have predictive importance for the effect of bevacizumab treatment.

8004 ORAL

Effectiveness of multiple lines of chemotherapy in platinum-resistant ovarian cancer: the Christie experience

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Background: Platinum-resistant ovarian cancer defined by a treatment-free interval of less than 6 months is characterised by chemoresistance with response rates in the range of 10−20% with non-platinum compounds. Higher response rates have been reported with combination chemotherapy from non-randomised studies although the effect on survival is uncertain. However the efficacy of multiple lines of chemotherapy in patients with platinum-resistant ovarian cancer remains to be determined. Crucially, is it appropriate to consider palliative chemotherapy in patients that have progressed through previous chemotherapy. Here we present data on over 150 patients treated sequentially with single-agent non-platinum compounds and combination chemotherapy.
Methods: Patients with platinum-resistant ovarian cancer treated with chemotherapy were extracted from the Christie ovarian cancer database. The regimens evaluated were Liposomal doxorubucin, Carboplatin/Liposomal doxorubicin, Cisplatin and oral Etoposide, weekly Paclitaxel, Gemcitabine/Platinum and Topotecan. Data were analysed for prognostic factors, response rates, toxicity, progression-free survival and overall survival.
Results: Majority of patients were stage III/IV at presentation and 80% had debulking surgery. Patients were evenly matched with respect to degree of tumour burden (> 2 sites of disease; tumour bulk> 5cms). Liposomal doxorubicin and the dose-dense weekly Cisplatin and oral Etoposide were used more commonly in 'early' platinum-resistant disease. The best response rates were seen with Carboplatin/Liposomal doxorubicin and the dose-dense cisplatin/oral etoposide regime. Progression-free survival and overall survival were significantly higher in the Carboplatin/Liposomal doxorubicin group perhaps indicative of its use early in platinum-resistant disease. On the other hand Topotecan was associated with negligible efficacy given its use in heavily pre-treated disease. The overall incidence of grade 3/4 toxicities was low. Mature data and full statistical analyses will be presented at the meeting.

	Liposomal doxorubicin	Carboplatin/ Liposomal doxorubicin	Cisplatin/ Etoposide	Paclitaxel weekly	Gemcitabine/ Platinum	Topotecan
Median age	64	65	65	71	65	60
Lines of chemo-median	2	2	2	2	3	3
Ca125 response GCIG criteria	30%	48%	43%	63%	33%	11%
Radiological Response	22%	37%	35%	24%	17%	0
Median PFS weeks (range)	21.5*	26.6*	17 (1−110)	18.5 (2−80)	15.5 (1−48)	13.5 (1−34)
Median OS weeks (range)	58*	58*	36 (1−147)	35 (3−88)	46 (2−130)	36 (4−116)

*Data (range) not mature, available by presentation

Conclusion: Multiple courses of chemotherapy are effective in platinum-resistant ovarian cancer.

8005 ORAL

Correlation of RNA expression of DNA repair genes with clinical outcomes of advanced ovarian cancer (OC) pts treated with pegylated liposomal doxorubicin (PLD) vs Trabectedin (T) + PLD in the ET743-OVA-301 clinical trial

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Background: Enhanced sensitivity to T has been observed in cells that, in addition to a proficient NER pathway, are deficient in homologous recombination repair (HRR). In a retrospective series, pts with soft-tissue sarcoma expressing high levels of ERCC1 and XPD [NER] and low levels of BRCA1 [HRR] experienced more favourable outcomes with T. These markers were prospectively investigated in available OC samples from the randomised Phase III study OVA-301.
Materials and Methods: Tumor tissue blocks from 183 consenting pts of the 672 OC pts enrolled in OVA-301 were analysed by qRT-PCR. 139 (76%) samples had at least one detectable expression level. High and low mRNA expressions were defined for levels above *vs* below the median, respectively. For progression-free survival [PFS] and overall survival [OS] association analyses to investigate outcomes by expression levels, and the relative benefit due to T depending on expression were carried out.
Results: Both in the overall study population (SP) and in the analyzed cohort, PFS and OS were significantly longer in the platinum (P)-sensitive *vs* P-resistant pts. In the SP, T+PLD induced a significantly longer PFS and a trend for longer OS than PLD. Pts with low BRCA1 mRNA levels had significantly longer OS ($p = 0.0297$) and PFS ($p = 0.0427$) than those with high BRCA1 levels, indicating the prognostic value of BRCA1 expression in the OC population studied. A trend ($p = 0.0765$) for longer OS (but not PFS) was found for pts with high ERCC1 expression levels. No significant differences in PFS or OS emerged for low or high XPD expression levels. PLD-treated pts with high ERCC1 mRNA levels tended to have longer PFS than those with low ERCC1 levels. No significant differences in PFS or OS were observed with the combined expression of BRCA1+ERCC1. Caveats of these analyses include low numbers of pts in each of the subgroups, prior P-based therapy in all pts (+ 80% prior taxanes) which might have modified the tumor RNA expression levels, immature OS data, and the effect of PLD added to T in the assessment of outcomes *vs* mRNA expression levels.

Conclusions: In this prospective study, low expression of BRCA1 and probably high expression of ERCC1 appeared to predict better prognosis in advanced relapsed OC. Unlike prior retrospective findings in T treated sarcoma, low BRCA1 and high ERCC1 levels did not predict longer PFS and OS in this trial. These results warrant further study to identify molecular biomarkers of outcomes with T therapy.

8006 ORAL

Improved outcome after first line chemotherapy in BRCA1- and BRCA2-associated ovarian cancer compared with sporadic ovarian cancer patients

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Background: Data of *in vitro* and small retrospective studies suggest that ovarian cancer (cells) without functional BRCA1 of BRCA2 proteins are more sensitive to DNA-damaging chemotherapy, such as platinum-containing regimens. In some clinical studies a better survival has been observed for BRCA1/2-associated versus sporadic ovarian cancer patients. Data, however, are not consistent; moreover, separate data for BRCA1- and BRCA2-associated ovarian cancer are lacking. Therefore, we compared response to, progression free (PFS) and overall survival (OS) after first line chemotherapy between BRCA1-associated, BRCA2-associated, and sporadic ovarian cancer patients, respectively.
Patients and Methods: From the database of the family cancer clinic, we selected 86 BRCA1 and 12 BRCA2 mutation carriers diagnosed with ovarian cancer between 1980 and 2008, and having been treated with chemotherapy. Patients were matched in a 1:2 ratio for year of birth and diagnosis (within 5-years periods) with 194 sporadic ovarian cancer patients. A Chi-square test was used to test for differences in type of responses, and Kaplan-Meier survival analysis to calculate PFS and OS.
Results: Mean age at diagnosis was 52 years. Stage III/IV was observed in 73%, and was not significantly different between the groups. First line chemotherapy mainly consisted of platinum-based regimens (96%). A complete (CR) or partial response (PR) was significantly more often observed in both BRCA1- and BRCA2-associated than in sporadic ovarian cancer patients (88% vs 100% vs 65%, respectively). The median PFS was significantly longer in BRCA1- (2.3 years, $p = 0.008$) and BRCA2-associated patients (2.9 years, $p = 0.03$) than in the sporadic group (1.4 years). Also, the 2- and 5-years PFS rates were significantly higher in the BRCA1- and BRCA2-associated groups than in the sporadic group, being 55% vs 58% vs 34%, and 33% vs 50% and 18%, respectively. The median OS was 6.2 yrs vs >10 yrs vs 3 yrs in the BRCA1, BRCA2 and sporadic groups, respectively ($p = 0.004$; and 0.009). In multivariate analysis, corrected for FIGO-stage and differentiation grade, the longer PFS and OS in the mutation carrier cohorts remained significant.
Conclusion: The response to, as well as the outcome after chemotherapy is significantly better in BRCA-associated than in sporadic ovarian cancer. Further, BRCA1- as well as BRCA2-associated ovarian cancer are different entities, with a trend for BRCA2 being most sensitive to chemotherapy.

8007 ORAL

Enhanced expression of Annexin A4 in clear cell carcinoma of the ovary and its association with chemoresistance to carboplatin

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Background: Clear cell carcinoma (CCC) of the ovary is known to be resistant to the platinum-based chemotherapy compared to serous or endometrioid adenocarcinoma of the ovary. Over 20% of all cases with ovarian cancer in Japan are classified as CCC and for unknown reasons this percentage is markedly higher (by approximately two-fold) than in Europe and the United States. The purpose of our study was to identify a candidate protein which is associated with chemoresistance of CCC, and to investigate the specific mechanism of chemoresistance conferred by the identified protein.
Materials and Methods: Two human ovarian cancer cell lines (OVISE-CCC/ OVSAHO-serous adenocarcinoma) were used for proteomic analysis. Enhanced expression of Annexin A4 was identified in ovarian CCC cells using 2-D differential gel electrophoresis (2D-DIGE) and mass spectrometry. Annexin A4 expression was further evaluated by real time RT-PCR and Western blot analysis using several ovarian cancer cell lines. Immunohistochemical analysis of Annexin A4 was performed in 126 epithelial ovarian cancer tissue samples. Chemoresistance (IC_{50} values) and intracellular platinum accumulation, following carboplatin treatment of Annexin A4-transfected non-CCC cells and empty vector control cells, were analysed by modified MTT assay and atomic absorption spectrophotometry.
Results: Annexin A4 levels were elevated in CCC cells compared with non-CCC cells as determined by real time RT-PCR and Western blot analysis. Immunohistochemical analysis demonstrated significantly high expression of Annexin A4 protein in ovarian CCC tumors compared with serous and endometrioid adenocarcinoma tumors ($p < 0.01$). Annexin A4-transfected cells were more resistant to carboplatin ($IC_{50} = 42$ mM) than control cells ($IC_{50} = 23$ mM). Intracellular platinum levels were significantly lower in Annexin A4-transfected cells compared with control cells following carboplatin treatment ($p = 0.0020$) and following an additional 360 min of carboplatin-free incubation ($p = 0.0004$).
Conclusion: Expression of Annexin A4 is elevated in ovarian CCC tumors and is associated with chemoresistance in cultured ovarian cancer cells. These results demonstrate that Annexin A4 confers chemoresistance in ovarian cancer cells in part by enhancing drug efflux. Annexin A4 may thus represent a novel therapeutic target of chemoresistance in patients with ovarian CCC.

Poster presentations (Tue, 22 Sep, 14:00−17:00)
Gynaecological cancer

8008 POSTER

Expression of inhibin/activin subunits (alpha, betaA and betaB) in normal and carcinomatous cervical tissue

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Background: Inhibins are dimeric glycoproteins composed of an alpha-subunit and one of two potential beta-subunits, (βA or βB), showing substantial functions in human reproduction and in endocrine-responsive tumours. In this study the expression of these different subunits was examined in normal and pathological cervical tissue.
Materials and Methods: Normal cervical tissue ($n = 10$) and cervical adenocarcinomas ($n = 6$) in archival specimens were examined by immunohistochemistry.
Results: Immunoreactivity of inhibin-α could be demonstrated in glandular cervical epithelium, while squamous epithelia cells did not express this subunit. Interestingly no analyzed cervical adenocarcinoma showed any staining reaction of this subunit. Both inhibin-βA and -βB subunits were seen in glandular epithelium of both normal and pathological cervical tissue. However, squamous epithelia cells also expressed these subunits, but with a lower intensity.
Conclusions: In this preliminary study we demonstrated an immunohistochemically detected expression of inhibin-α, -βA and -βB subunits in normal as well as in pathological cervical specimens. Possibly inhibin molecules are useful serological markers in cervical cancer. The subunits are expressed immunohistochemically to a certain amount, thus suggesting possible functions in normal and pathological cervical tissue. Moreover, inhibin-alpha is considered a tumour suppressor in several gynaecological malignancies, including endometrial and ovarian cancer. If this holds also true for cervical cancer will be evaluated in future studies.

8009 POSTER

Human papillomavirus type16 (HPV16) E6 gene variations in cervical intraepithelial lesion from Thai women

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HPV16 infection is found as a major risk factor for cervical cancer in Thai women. Variations of HPV16 E6 gene that lead to amino acid changes may be associated with increased oncogenicity. This study aimed to investigate