943 POSTER

Phase II study of Sorafenib (BAY 43–9006) in combination with Gemcitabine in recurrent epithelial ovarian cancer –a study of the PMH phase II consortium

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Background: Sorafenib is a novel multi-targeted tyrosine kinase inhibitor that targets RAF/MEK/ERK signaling pathway, vascular endothelial and platelet derived growth factors receptors and flt-3. Phase I studies have demonstrated safety and tolerability of sorafenib in combination with gemcitabine, with preliminary activity seen in recurrent ovarian cancer. VEGF is over expressed in human ovarian tumors and is associated with poor prognosis and development of ascites. Therefore sorafenib and gemcitbine would make a rational therapeutic strategy for combination in recurrent ovarian cancer.
Methods: A Phase II, two stage clinical trial in women with recurrent ovarian cancer who have received upto 2 prior lines of chemotherapy following recurrence is underway, assessing the activity of sorafenib 400 mg bid continuously in combination with weekly Gemcitabine 100 mg/m^2. Cycle 1 is an extended cycle of 7 weeks of G followed by a break for a week. Subsequent cycles are 4 weekly with G being administered for the first 3 weeks of each cycle. Twenty one patients have been enrolled to date; 14 are evaluable for toxicity having received 18 cycles of treatment and 9 are evaluable for response.
Results: Of patients evaluable for response, one patient has had a confirmed response and 8 patients had stable disease. Grade 3 toxicites that have been seen in more than one patient to date are pain (3), lymphopenia (5), thrombocytopenia (3), leucopenia/neutopenia (2) hand foot (2) and biochemical transaminitis (2).
Conclusions: This trial continues to accrue. Updated results will be presented.

944 POSTER

Hormone replacement therapy in cervix cancer survivors: is it safe?

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Introduction: The young patients with cancer of cervix will go into early menopuause due to surgery and adjuvant/or radiacal radiotherapy. In moste cases the oncologists would advised these women against the use of HRT. The purpose of this study was to evaluate the influence of HRT on the well being and the reccurence of squamous cell cevix carinoma in women treated with surgery and adjuvant or radical radiotherapy.
Materials and Methods: From 1992 to 2003, HRT was prescribed for 136 premenopause pts with cervix carcinoma St Ib1 to St IIIb. Each pts from HRT group was compared with pts from the group with same diagnosis who did not received HRT. The meching crieteria were: ageand, stadium of disease and DF interval until applying HRT. All patients had squamous cell cervix carcinoma Mean age was 32 years (rang 23–39years). Baseline mammography and/or brest ultrasound were performed in 136pts before starting HRTand control group. In HRT group 67/136pts underwent radical hysterectomy and adjuvant radiation due to carcinom of the cervix ST Ib1(>2 cm)and ST IIa. 69/136pts had radical radiation therapy for St IIb-IIIb cervix cancer. To relieve climacteric symptoms and to prevent osteoporosis mono-estogenes therapy (transdermal-67/136pts) and continuos combined HRT (E2/NETA-(45/69pts) and tibolone (24/69pts) were prescribed. The mean duration of treatment was 4.7 (rang 1.4–12.3 years).
Results: HRT is extremely effective in amelioratiomg the vasomotor symptoms associated with early menopause (136/136pts vs 91/136, $p < 0.001$). Vaginal dryness, dyspareunia and recurrent urinary tract infections are effectively treated with HTR (116/136pts vs 100/136, $p < 0.001$ (32/45pts receiving E2/NETA had an apparent increase in brest density, whereas no changes was recorded in patients on E2 and tibolone or without HRT. No other clinically significant abnormalities were observed. Brest pain was often reported as an adverse event in the E2/NETA(39/45pts) and tibolone group (19/24 pts) vs 48/136 pts no HRT, retrospecively. Normal baseline bone-mineral density had 127/136 pts. vs 119/136pts. Bone-osteodensitometry showed osteopeny in 6 pts before HRT (these patients were menopause 6.7 years; (Bone–mineral density increased in 5/6pts who received E2/NETA and tibolone. BMD after 5 years of treatment: osteoporosis 2/136 vs 36/136, $p < 0.001$. DFS was 86% in the group on E2 vs 82% no HRT ($p > 0.001$) and 65% in the group on E2/NETA or tibolone vs 61% ($p > 0.001$)
Conclusion: there is no evidence that HRT influence on development of the local or distant recurrences in the patients with the cervix carcinom in contrast to well-being.

945 POSTER

Efficacy of pegylated liposomal doxorubicin (PLD) plus carboplatin in patients with intermediate sensitive relapsing advanced ovarian cancer

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Background: The goal of first line chemotherapy in advanced ovarian cancer is to induce complete response in order to induce durable response and long progression free interval and even a cure. However, in relapsing disease, palliation and quality of life become very important goals as the chance for a cure becomes less probable. While single agent PLD (Caelyx®) is the treatment in some patients in early relapse <6 months and paclitaxel+carboplatin combination is well established in late relapse >12 months; The optimal therapy for the 6 and 12 months population still remains to be defined. The GINECO group showed that PLD+carboplatin can induce a high response rate with less alopecia, neuropathy and myelosuppression than the paclitaxel+carboplatin combination.
Methods: A multi-center single arm phase II trial to assess the safety and efficacy of PLD 30 mg/m^2 in combination with carboplatin AUC 5 mg/ml/min every 4 weeks was undertaken. Eligibility criteria included: Measurable disease, prior taxane and platinum regimen with a progression free interval >6 months and <12 months. The study is planned of 63 patients and the primary objective is response according to the RECIST criteria. Secondary objectives are duration of response, time to progression, safety and overall survival.
Results: Thirty-four patients have been enrolled and are the subjects of this early report, median age 61 years (44–80). Median progression free interval before entering the study is 37 weeks (26–52) with a median of 8 prior cycles (4–9) of paclitaxel carboplatin. No major toxicity has been reported; Only 3 grade 3–4 toxicities were reported: Anemia, abdominal pain and allergic reaction. The incidence of hand foot syndrome (HFS) is relatively low with no grade 3–4. Other toxicities were uncommon and usually did not lead to discontinuation of therapy. An early efficacy analysis revealed a 40% objective response rate with 36% of patients having stable disease. Median time to progression is 30.5 weeks with more then 40% still progression free.
Conclusion: The combination of PLD with carboplatin given every 4 weeks in the intermediate sensitive patients is active and well tolerated. This combination gives an interesting efficacy while minimizing toxicity in this difficult to treat patient population.

946 POSTER

Protective role of the polymorphism CCR2–64I in the progression from squamous intraepithelial lesions to invasive cervical carcinoma

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Background: Invasive cervical cancer (ICC) is one of the most common malignant diseases among women, representing almost 10% of all the cancers in the female population. The aim of this study was to explore the association of the *CCR2–64I* polymorphism with the risk of developing Invasive Cervical Cancer (ICC).
Methods: DNA samples were extracted from peripheral blood cells of 109 patients with squamous intraepithelial lesions (SIL) and 217 patients with ICC. The *CCR2–64I* polymorphism was analyzed through PCR-RFLP (BseJI). Analysis of data was performed using the computer software SPSS for windows. The odds ratio (OR) and its 95% confidence interval (CI) were calculated as a measure of the association between *CCR2–64I* genotypes and cervical cancer risk.
Results. The frequency of the G/A genotype was significantly higher in SIL patients (n = 109) than in ICC patients (n = 217) ($p = 0.005$; OR = 0.42; 95%IC: 0.22–0.83).

Conclusion: These findings suggest that *CCR2−64I* polymorphism has a protective role in the evolution from SIL to ICC.

947 POSTER

Molecular defects in endometrial carcinomas: microsatellite instability (MSI), PTEN and beta-catenin gene mutations.

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Background: In order to better understand the molecular pathogenesis of sporadic endometrial carcinomas, we assessed the frequency of incidence of microsatellite instability (MSI) and mutations in PTEN and beta-catenin gene and analyzed detected defects in relation to each other and to clinico-pathological features of endometrial carcinomas.
Material and methods: Material included DNA from 59 endometrial carcinomas, all but two are endometrioid type, and from blood lymphocytes of the same patients. Mutations were assessed in all nine exons of PTEN gene and in exon 3 of beta-catenin gene by PCR-SSCP and sequencing methods. The analysis of MSI was carried out using eight DNA microsatellite markers by PCR with fluorescent-labelled primers and electrophoresis in polyacrylamide gel.
Results: In 30 carcinomas (50.8%) mutations were found in PTEN gene and in 9 tumors (15%) in beta-catenin gene. Microsatellite instability (MSI+) was identified in 19 carcinomas (32.2%). The remaining 40 tumors (67.8%) was stable DNA (MSI−). In 17 cases (28.3%), in the studied microsatellites a loss of heterozygosity (LOH) was also revealed. The following relations were observed between the detected defects. In MSI+ tumors, PTEN mutations occurred significantly more frequently than in MSI− tumors (73.7% vs 40%, $\alpha = 0.0094$) but, except for one, none of PTEN mutations was characteristic for MSI. In contrast, no significant differences were found in frequency of incidence of beta-catenin gene mutations in MSI+ and MSI− tumors (15.8% vs 15.0%, $\alpha = 0.785$). Interesingly, mutations in beta-catenin gene most frequently coexisted with mutations in PTEN (7/9; 77.8%). PTEN and beta-catenin gene mutations as well as MSI were more frequent in early clinical stages as compare to advanced tumors, although these differences did not reach statistical significance. However, statistically significant, reverse correlations were observed between the frequency of PTEN gene mutations or MSI and the grade of morphological differentiation of the tumors (G3 vs G2+G1, $\alpha = 0.033$ and 0.023, respectively) and the age of women (before vs after age of 60, $\alpha = 0.044$ and $\alpha = 0.065$, respectively).
Conclusions: The results of this study suggest that most frequently occurring mutations in PTEN gene may play crucial role in endometrial carcinoma pathogenesis. The coexistence with them or absence of mutations in beta-catenin gene or MSI may reflect the heterogeneity of molecular mechanisms of development of endometrial carcinoma.

948 POSTER

Fc-gamma, RIIa-131RH polymorphism is associated with decreased risk for the development of cervical lesions

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Background: The infection by HPV is the necessary cause for the development of cervical cancer and the clinical course of the disease is mainly influenced by immunological responses. The IgG response is associated with both squamous intraepithelial lesions (SIL) and cervical (CC) cancer, and it is barely induced in the preclinical infection. The Fcã receptors of the IgG play an important role, coupling the humoral and cellular immune responses, and their described polymorphisms may influence the immune responses due to the higher or lower affinity of the receptor for the IgG molecule.
Material and methods: The FcãRIIa H/R polymorphism was analysed in 310 individuals: 200 women with cervical lesions and 110 healthy women, by PCR-RFLP.
Results: In this preliminary study, we observed statistically significant differences between the heterozygous genotype HR in cases and controls (OR = 0.535, CI95% [0.326−0.876], p = 0.012) and this difference is highly stronger when we compare women with SIL lesions and the healthy group, regarding the HR genotype (p = 0.00012; OR = 0.143, 95% CI [0.048−0.425]).
Conclusions: Our results suggest that the presence of the FcãRIIa HR genotype has a protective role for the development of pathologies of the uterine cervix, especially in the case of SIL.

949 POSTER

Antiangiogenesis as new treatment modality in ovarian cancer: a phase Ib, open label, safety and pharmacokinetics (PK) study of escalating doses of PTK787/ZK222584 (PTK/ZK) in combination with paclitaxel and carboplatin in patients (pts) with stage IC to IV epithelial ovarian cancer

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Background: Vascular endothelial growth factors (VEGFs) and VEGF receptors (VEGFRs) are important mediators of tumor growth and metastasis and their expression is associated with poor prognosis in epithelial ovarian cancer. PTK/ZK is a novel, oral, angiogenesis and lymphangiogenesis inhibitor that blocks tyrosine kinase signaling from all known VEGFRs.
Methods: An open-label, multicenter, phase-IB, dose-escalation study evaluated PTK/ZK with chemotherapy as first line-therapy in pts with stage IC-IV epithelial ovarian cancer. Paclitaxel was administered as a 3-hour infusion on day 1 of each 21-day cycle at 175 mg/m^2. Carboplatin was given immediately after paclitaxel as a 30-min IV infusion to an AUC of 5 mg min/mL. PTK/ZK was given daily from day 3−21 of each cycle. Cohorts of 3 to 6 pts received doses of PTK/ZK at 250, 500, 750, 1,000 or 1,250 mg/day. MTD and DLT of PTK/ZK were assessed; PK of PTK/ZK, carboplatin and paclitaxel was characterized.
Results: 19 pts were evaluated; 16 for DLT; 18 for PK. No DLTs or PTK/ZK-related SAEs were reported. One pt discontinued due to AEs. Grade 1−2 hypertension was the most common AE. Steady-state PTK/ZK plasma levels were constant between cycle 1−2. PTK/ZK has no impact on systemic exposure of free platinum. Paclitaxel exposure was not affected at the biologically active dose of 1,250 mg/day PTK/ZK. Additional data are being collected at the 1,250 mg dose level.
Conclusion: PTK/ZK with paclitaxel and carboplatin is feasible and shows acceptable safety. Updated data will be presented.

950 POSTER

The prognostic significance of c-erbB-2, p53 and bcl-2 immunoexpression in patients with epithelial ovarian cancer treated with paclitaxel and platinum

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Background: Several oncogenes and oncosuppressor genes have been implicated in epithelial ovarian carcinogenesis, but their clinical significance is not clear and several conflicting data are found in various studies.
Material and methods: We investigated the immunohistochemical expression of c-erbB-2, p53 and bcl-2 proteins in a cohort of 95 patients with advanced epithelial ovarian cancer (stage IIc-IV), who participated in a phase III randomized clinical trial and were treated by either paclitaxel plus carboplatin or paclitaxel plus carboplatin alternating with cisplatin. The immunohistochemical expression profiles were correlated with conventional prognostic parameters, remission status after first line chemotherapy and overall survival at uni- and multivariate levels.
Results: Positive immunostaining for c-erbB-2, p53 and bcl-2 proteins was found in 68%, 71% and 69% of the cases respectively. In multivariate analysis, age (<63 vs.⩾63 years, p = 0.016), remission status after first line chemotherapy (patients in complete remission vs. all others, p < 0.001) and p-53 expression (negative vs. positive, p < 0.001) were found to be the only significant prognostic factors independently associated with overall survival.
Conclusions: p-53 status along with age and complete remission status after first line chemotherapy appear to be independent prognostic factors for overall survival in patients with epithelial ovarian cancer. Surprisingly, p53 positive expression was correlated with improved survival.