Materials and Methods: ZK-EPO was compared with paclitaxel and the epothilones ixabepilone and epothilone B for its ability to inhibit proliferation in a range of human tumour cell lines. Activity against OC in vivo was assessed in tumour xenografts in SCID mice.
Results: ZK-EPO demonstrated sub-nanomolar IC_{50} values for established OC cell lines, including the A2780 and multidrug-resistant A2780/Adr OC cells, unlike ixabepilone, epothilone B and paclitaxel. In vivo, ZK-EPO showed significant dose-dependent inhibition of OVCAR-3 and OVCAR-8 tumour growth compared with paclitaxel and cisplatin. In tumour cell cultures newly isolated from OC patients, ZK-EPO displayed a high level of activity against all 27 isolates tested, and was significantly more active than paclitaxel and docetaxel, and the epothilones ixabepilone, epothilone B and KOS-862. This was clearly evident after only 1 h exposure, when the mean IC_{50} across the 27 isolates was 4 nM (epothilone B), >50 nM (docetaxel), >60 nM (paclitaxel), >90 nM (ixabepilone) and >100 nM (Kos-862). After 3 days, ZK-EPO showed sub-nanomolar IC_{50} values for all isolates tested, compared with higher nanomolar IC_{50} values for the other agents. These effects were seen irrespective of the parent tumours' clinical response to platinum-containing therapy. Xenograft models from a number of primary OC cell lines were established in SCID mice, and their sensitivities to treatment correlated with those of in vitro models.
Conclusion: ZK-EPO is highly active against all OC tumour model systems examined in vitro and in vivo. Importantly, all newly isolated patient-derived OC cell lines tested have been sensitive to ZK-EPO, which has demonstrated significantly higher antiproliferative activity than comparator compounds such as ixabepilone, Kos-862 and paclitaxel, even after short-term exposure. ZK-EPO is now in Phase II clinical trial in patients with OC.

5010 ORAL

Phosphorylated 4E binding protein 1 (p4EBP1) correlates with pathologic grade and prognosis in cervical cancer treated with surgery and radiation therapy

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Purpose: To assess the prognostic value of phospho-4E binding protein 1 (p4EBP1) in cervical cancer patients treated with surgery and radiotherapy. p4EBP1 is a signaling molecule downstream of mTOR and ERK pathways that may integrate membrane-generated signals and promote cellular proliferation.
Methods: Upon revision of medical records, 66 women who underwent surgery and adjuvant radiotherapy at our institution between 1996 and 2004 for early stage cervical cancer were identified. 13 patients received concomitant chemotherapy. Tumor tissue blocks were cut and immunohistochemically stained for expression of p4EBP1. The extent and intensity of staining were measured and an immunohistochemical store determined. Survival curves were generated and the outcome compared by the log-rank method.
Results: 66 patients were evaluated. Median follow-up was 24 months and median age was 58 years. Histologic type was squamous cell, adenocarcinoma, adenosquamous and other in 33, 26, 3 and 4, respectively. FIGO stage was IA, IB and II in 1, 46 and 19 patients, respectively. High-level expression of p4EBP1 was identified in 53% of samples. Freedom from local recurrence was significantly poorer in tumors with high-level expression of p4EBP1 ($p = 0.034$). No impact of p4EBP1 on metastatic disease was observed. High-level expression of p4EBP1 was significantly associated with cancer-specific survival ($p = 0.037$). Interestingly, higher levels of p4EBP1 were observed in poorly differenciated tumors ($p = 0.044$).
Conclusion: In this study, expression of p4EBP1 was significantly associated with high-grade tumors and poor prognosis in cervical cancer patients treated with surgery and radiation therapy. Further evaluation of this factor may help understand the oncogenic role of p4EBP1 in cervical cancer.

5011 ORAL

COX-2 polymorphism and susceptibility to gynaecological malignancies: −765C allele confers increased risk for ovarian cancer

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Background: Invasive cervical cancer (ICC) and Ovarian cancer (OC) are the most frequent malignancies among women worldwide (almost 14% of all newly diagnosed cases). Although the etiology underlying OC in not fully understood, unlike ICC, in both neoplasias chronic inflammation plays an important role in the onset of the disease. Cyclooxygenase-2 (COX-2) is highly inducible by growth factors, tumor promoters and has an important role in the inflammatory process, as well as in key steps of tumor development. Several polymorphisms in COX2 have been identified, although only a few appear to influence the susceptibility to cancer development. The 765G>C COX2 polymorphism, in the Sp1 binding site of the gene's promoter region, has been associated with the development of several diseases. The aim of our study was to assess the influence of this polymorphism in the development of OC and ICC.
Materials and Methods: This cross-sectional study involved 727 women, 150 of which had ovarian adenocarcinoma and 351 cervical lesions (60 squamous intraepithelial lesions and 291 invasive cervical cancer). The remaining 226 women had no evidence of malignant disease (control group). The 765G>C COX2 polymorphism genotypes were determined by PCR-RFLP.
Results: We found no statistically significant differences in the distribution of the 765G>C COX2 polymorphism genotypes between ICC cases and controls ($p = 0.879$). The frequency of the −765GG, GC and CC genotypes were, respectively, 64%, 31% and 5% in controls and 49%, 47% and 4% in women with ovarian cancer. We observed that women with GC and CC genotypes had a nearly two-fold increased risk for development of OC ($p = 0.004$; OR = 1.8; 95% CI: 1.211−2.787). This susceptibility was even higher, nearly 3-fold, when considering women younger than or with 53 years ($p < 0.0001$; 95% CI = 1.623−4.838).
Conclusion: The −765C allele seems to increase the susceptibility to develop OC, especially in women younger than or with 53 years. The different influence that this polymorphism seems to have on the onset of OC and ICC could be explained by the distinct etiologies of both cancers. The role of −765GC COX2 polymorphism in the susceptibility to ovarian cancer could be due to an enhanced expression of COX2 by the −765C allele that will promote an increased inhibition of apoptosis, enhanced tumor proliferation, angiogenesis and metastasis.

Poster presentations (Wed, 26 Sep, 14:00−17:00)
Gynaecological cancer

5012 POSTER

Durable clinical responses with autologous dendritic cells pulsed with MUC1: a phase II trial in ovarian carcinoma patients

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Background: The Mucin 1 (MUC1) glycoprotein is highly expressed by ovarian carcinoma and is thus a potential antigen for an immunotherapy approach. We report a phase II trial in patients (pts) with ovarian carcinoma treated with dendritic cells (DC) pulsed with mannan-MUC1 fusion protein (DC-MFP), following successful phase I results in similarly treated patients [1].
Methods: Eligibility criteria were: incurable disease; age >18 yrs; PS 0−2; no autoimmune disorders; rising CA125 levels (>25% in 1 mth, confirmed). The primary endpoint was CA125 response: major response >50% reduction, minor >25% (each confirmed at 4 wk) or stabilisation (>3 mths). PBMC were collected by leukapheresis, cultured with IL-4 and GM-CSF to generate DC, and pulsed with MFP on day 5. DC were reinjected on day 6 as i.d. injections to 8 body sites (each 5×10^6), given 4-weekly $\times$ 3, then 10-weekly to 12 months. Excess cells were cryopreserved for subsequent injections.
Results: 28 pts were recruited, with all evaluable for toxicity and 21 for efficacy (received at least 3 vaccinations). Characteristics were: serous histology 24 (86%) pts; 88% of tumours were MUC1+ on IHC; median age 58 yrs (34−78); PS 0−1 27 (96%) pts; prior systemic therapy (all pts platinum-treated) 1 line 5 pts, 2 lines 4 pts, 3 lines 10 pts, 4 or greater lines 9 pts. Leukapheresis was generally required only 6-monthly. Following ex vivo culture, the proportion of CD86+ cells ranged from 40−85%. There was no grade 3 or 4 therapy-related toxicity. Of 21 pts, 4 (19%) showed CA125 response or stabilisation. 2 pts had major response: 1 pt with 4 previous lines of systemic therapy (received DC-MFP 12+ mths) and 1 pt treated second line (duration 14 mths). One pt had stable disease of 7 mths duration which included 10 wks classified as minor response and one pt, treated fifth-line, had stable disease for 5 mths. An additional pt, treated fourth-line, had >25% CA125 reduction which was not confirmed by repeat