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

CA125. CT scan results were generally concordant with CA125 status. No relationship was seen between clinical benefit and HLA type.
Conclusions: Study treatment was well tolerated. There was clear evidence of clinical benefit for some pts, including pts who were heavily pre-treated. This DC-MFP approach warrants further study in patients ovarian carcinoma.
Supported by grants from PrimaBiomed Ltd.

References

[1] Loveland et al. Clin Cancer Res 2006; 12: 869.

5013 POSTER

Squamous cell carcinoma antigen level as a prognostic factor for uterine cervical carcinoma from Korean Patterns of Care Study 1998–1999

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Background: The aim of this study is to verify prognostic factor of initial serum squamous cell carcinoma (SCC) antigen level as a tumor marker for uterine cervical carcinoma patients with squamous cell carcinoma histology. All the patients received radical radiotherapy and the data were collected from web-based Korean Patterns of Care Study (PCS) 1998–1999 program.
Materials and Methods: We conducted a nationwide on-line data entry of uterine cervical cancer after completion of web-based Korean PCS program (http://www.pcs.re.kr) Of the whole 42 hospitals operating at that time (1998–1999 year) 33 institutions participated the study. Selection of the patients in each hospital was based on randomized sampling process. External audit of the on-line record was reviewed and confirmed by trained central data manager visiting each hospital. The data of 647 patients were reviewed and 400 patients underwent serum SCC antigen level evaluation at diagnosis. We analyzed the treatment outcome of the patients according to SCC level.
Results: The median age of the 400 patients was 61 years old (range 28−86) and 55% (210 patients) of the patients were FIGO stage IIB. Pre-treatment serum SCC antigen level were in the range of 0.1–369 ng/ml. The positivity rate (2.0 ng/ml or more) was increased with FIGO stage. Number of the patients with normal SCC was 115, mild elevation (2.0−4.9 ng/ml) 105, moderate (5.0−19.9 ng/ml) 116, and severe 64. After radiotherapy, 91% of patients with the elevated SCC level were normalized. Thirty five patients developed locoregional relapse and 73 patients had distant metastasis as first event during follow-up period. The 5 year relapse free survival rate (5YRFSR) for FIGO I, II, III, and IV were 92.1%, 61.5%, 31.0%, and 30.0% respectively. The 5YRFSR according to SCC level were 74.5% for normal, 64.1% for mild elevation, 47.0% for moderate elevation, and 58.6% for severe elevation ($p = 0.0005$). By multivariate analysis, initial SCC level was still a prognostic factor ($p = 0.022$).
Conclusions: initial SCC assay is a useful aid to predict the prognosis of squamous cell carcinoma of the uterine cervix. For patients with moderate to severely elevated SCC level (>5.0 ng/ml), more aggressive treatment including higher radiation dose and/or intensive concurrent chemotherapy is needed for better disease control. We recommended that SCC antigen assay and monitoring during follow-up is necessary from the results of Korean PCS 1998–1999 for uterine cervix cancer.

5014 POSTER

Evaluations on the natural history of human papillomaviruses infections and related diseases in HIV-seropositive women

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Background: Convincing evidence has been accumulated that human papillomaviruses (HPV) are the most important risk factor for cervical carcinogenesis also in women infected with human immunodeficiency virus (HIV-seropositive). So far, long-term follow-up of patients with bordeline changes has been difficult to achieve. Thus, the see-and-treat management paradigm was used. Introduction of highly active antiretroviral therapy (HAART) allow a longer patient survival and a more detailed analysis of opportunistic pathologies HIV-associated.
We documented the impact of HAART on the natural history of HPV infections testing specimens by polymerase chain reaction (PCR) with two pairs of primers (MY09/MY11 and GP5*/GP6*) and DNA sequencing.
Material and Methods: From September 2002 throughout January 2005, 379 patients were enrolled at the University of Brescia. Cases are selected at preliminary gynaecological visit as low-grade abnormality. The patients were followed-up by cytology and colposcopy at 6 months intervals and referred for biopsy in cases of persistent or increasing abnormalities. All women had PCR tests at 0, 6, 12, 24, 36 months and a colposcopic-directed biopsy at the endpoint.
Results: At baseline, cytological diagnoses showed 182 smears (48%) within normal limits, 109 ASCUS (29%), 68 low-grade SILs (18% LSIL) and 20 high-grade SILs (5% HSIL). The median CD4 cell count at inclusion was 250/mm^3. The overall HPV DNA high-risk positivity detected was 73% by PCR in the categories of ASCUS/LSIL/HSIL and 12% in the normal specimens. After 1 year, 199 HIV-patients were lost, in the remaining 180 women, the high-risk DNA positivity was maintained in the 58% of samples while 12 patients (7%) showed a cyto-histological progression. In the 110 patients followed-up at 24 months the overall HPV positivity was 52% and 13 showed a cyto-histological progression to high-grade neoplasia. At the end-point only 15 of 105 women (14%) had biopsy-confirmed CIN3.
Conclusions: Nowadays, timely treatment by HAART confers a substantial improvement in curative potential and live cost savings of patients. Meanwhile higher reliability of PCR techniques has substantially increase the detection rate of incoming HPV infections with acceptable positive predictive values. Our studies revealed that HAART modified the course of CIN in HIV-infected women by significantly reducing HPV positivity and increasing the reversion of the low-grade abnormality to normality. Fine data on the impact of HAART on the different cervical HPV lesions will be presented.
This study was funded by AIRC programme 2001 and by Ministero della Salute, Programma per la Ricerca Sanitaria 2003.

5015 POSTER

The usage of expression profiles of p53, delta Np63, and delta Np73 as prognostic markers in invasive cervical carcinoma

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The tumor-suppressor protein p53 has been shown to belong to a family that includes two structurally related proteins, p63 and p73. In contrast to p53, p63 and p73 encodes truncated N-terminal isoforms of p63 (delta Np63) and p73 (delta Np73) which can inhibit the transactivating function of full length isoform. In this study, we investigate the correlation between the inactivation of p53 protein via the presence of oncogenic viral E6 and the overexpression of delta p63/p73 isoforms in 33 invasive cervical carcinoma. Overexpression of p14 and p16 will be used as indicators for the inactivation of p53 and pRb by HPV oncoprotein E6 and E7. Immunostaining of p14, p16, delta Np63 and delta Np73 will be compared to the cervical staging and HPV status using 20 normal cervix as control. Overexpression of p14, p16 delta Np63 and delta Np73 are statistically increased comparing to normal cervix with p value (Mann-Whitney test) of <0.001, <0.001, 0.002 and <0.001, respectively. Our results clearly showed that overexpression of p14 and p16 is well correlated to the presence of integrated HPV, while negative staining was found in normal cervix. Interestingly, inactivation of p53 protein was found to correlate with up regulation of delta p63 ($p < 0.001$) but not delta p73 (0.454). Moreover, expression profiles of p14, p16, deltaNp63, and deltaNp73 demonstrated statistically associated with clinical staging using Mann-Whitney test at $p < 0.001$, $p < 0.001$, $p = 0.004$ and $p < 0.001$, respectively. Our study suggested that loss of functional p53 protein might enhance p63 expression leading to increase deltaNp63 isoform. Outcome of the followed-up cases will also be analyzed in order to evaluate its possible potential as prognostic profile in cervical cancer treatment.

5016 POSTER

A prospective study of MR imaging prognostic factors in women with cervix cancer treated with chemo-radiation

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Purpose: Chemo-radiation (CRT) has become the standard of care in women with locally advanced cervix cancer. The use of MRI as part of the staging investigations makes it possible to accurately estimate the volume and relations of the tumor, as well as the presence of lymph nodes. Further improvements in patient outcome will depend on a better understanding of the causes of pelvic and systemic relapse and the use of predictive prognostic factors to individualize treatments. The knowledge of these factors through modern imaging could be used for selecting the optimum treatment modality while minimizing side effects.