(tumour, uterus, upper vagina and parametria) and OAR were contoured on the fused axial MR-CT images, and on each subsequent weekly scan. Two IMRT plans were generated on the baseline images, a large margin IMRT plan (LM) using a 2 cm PTV margin around except 1 cm inferiorly and a small margin IMRT plan (SM) using a 5 mm PTV margin only. Contours were converted to 3D surface meshes, which were used to derive an anatomic deformation model for each tissue based on biomechanical principles. Patient anatomy at each fraction was translated to the baseline case, allowing the dose impact of inter-fraction motion to be modelled for the tumour and each OAR. A replan (RM) was done after the second week of radiotherapy as part of an individualized adaptive strategy, using a new PTV, based on information from the prior weekly scans. IMRT optimization objectives for the replan were specified to the new PTV and OAR from the second weekly scan. All treatment planning and deformable dose accumulation was performed using a research software package.
Results: Of the twenty-five patients in this study, a sub-set of ten, have been analysed to date. When inter-fraction motion was modelled and the accumulated dose to the target was assessed, at least 98% of the CTV was covered by the 95% isodose for LM, SM and RM plans, with a trend to improved coverage in some patients with RM. Median accumulated dose to OAR was significantly reduced with SM and RM compared to LM ($p < 0.05$ for rectum, bladder and bowel). A further reduction in median accumulated dose to rectum (4711 cGy vs 4549 cGy, $p = 0.03$) and sigmoid (4716 cGy vs 4611 cGy, $p = 0.02$) was seen with RM compared to SM.
Conclusion: In spite of inter-fraction motion, the use of smaller planning margins (5 mm) results in acceptable target coverage and reduces dose to OAR. The addition of one adaptive replan in the course of treatment resulted in a further significant reduction in dose to OAR, and did not compromise CTV coverage.

5031 POSTER

Combination chemotherapy with carboplatin and gemcitabine in patients in platinum-resistant ovarian cancer chemotherapy: a phase II study demonstrating inhibition of DNA cross-link repair by gemcitabine

J.A. Ledermann[1], H. Gabra[2], G.C. Jayson[3], V.J. Spanswick[1], G.J. Rustin[4], M. Jitlal[1], L.E. James[1], J.A. Hartley[1]. *[1]University College London, Oncology, London, United Kingdom; [2]Hammersmith Hospitals, Oncology, London, United Kingdom; [3]Christie Hospital, Oncology, Manchester, United Kingdom; [4]Mount Vernon Cancer Centre, Oncology, Northwood, United Kingdom*

Background: Synergy between platinum and gemcitabine has been demonstrated in preclinical models, but not in humans. We have studied the tumour response adding gemcitabine to carboplatin in 'platinum-resistant' ovarian cancer and performed a pharmacodynamic study of the effect of gemcitabine on the ability of cells to repair platinum-induced DNA cross-links.
Methods: 40 patients (pts) relapsing with a treatment free interval of <6 months received carboplatin AUC4 followed by gemcitabine 800 mg/m^2 D1 and 8, every 3 weeks for up to 6 cycles. In 12 patients blood samples were taken, pre chemotherapy, post carboplatin infusion, and immediately after gemcitabine. On D 8 patients received gemcitabine alone with samples taken pre- and post-infusion. Peripheral blood lymphocytes were isolated and incubated ex vivo for varying lengths of time. Carboplatin-induced DNA interstrand cross-link formation and repair was assessed using the Single Cell Gel Electrophoresis (Comet) assay. Tumour response was measured by changes in CA125 (Rustin criteria) and CT imaging.
Results: Data on 38 pts are available. 55% had 1 prior platinum therapy, 21% 2 and 13% >2 courses of treatment (10% data awaited). 167 cycles were given (median 5 per pt). Haematological toxicity was the main dose-limiting factor. 22% of cycles were delayed ($\geqslant$28 days between cycles) and 65% pts $\geqslant$1 delay. D8 gemcitabine was omitted in 19% of cycles (53% of pts did not receive at least 1 D8 chemotherapy). CA125 response is available for 29 pts; 11 (38%) responded (10 and 1 with a 75% or 50% response respectively). Twenty four pts had CT evaluable disease. 4 (17%) PR; 8 SD; 12 PD; 14 pts had non evaluable or inevaluable (1 death, 6 <3 cycles, 3 unknown). The peak of DNA interstrand cross-linking was seen 24 hours post-incubation. After carboplatin alone, repair of cross-links at 48 hours in 12 samples was 81% (100% repair in 8, the remainder were 77, 75, 19 and 0% repair). In the same patients following gemcitabine, repair of DNA cross-links was significantly reduced (median 21.5%). 5 patients showed no repair at 48 hours and in 7 repair ranged from 7 to 60%. No single strand breaks were seen in any patient following gemcitabine alone.
Conclusions: These data demonstrate that the combination of gemcitabine and carboplatin is active in platinum-resistant ovarian cancer and that the addition of gemcitabine inhibits the repair of in vivo induced carboplatin-DNA cross-links. Updated results will be presented.

5032 POSTER

Phase I/II trial of external irradiation plus medium-dose brachytherapy given concurrently to liposomal doxorubicin and cisplatin for advanced uterine cervix cancer

E. Petinellis[1], M. Mazonakis[2], S. Kachris[1], E. Lyraraki[1], A. Varveris[1], A. Fasoulaki[1], A. Tzedakis[2], M. Xenaki[1], V. Kouloulias[3], C. Varveris[1]. *[1]University Hospital of Crete, radiotherapy-oncology, Heraklion, Greece; [2]University Hospital of Crete, medical physics, Heraklion, Greece; [3]University Hospital of Attikon, radiotherapy-oncology, Athens, Greece*

Background: Although the standard of care for patients with locally advanced uterine cervix carcinoma is cisplatin (CDDP) – based chemotherapy and irradiation (RT), the optimal regimen remains to be elucidated. A phase I/II study was conducted to evaluate the dose limiting toxicity (DLT) and the maximum tolerated dose (MTD) of liposomal doxorubicin (Caelyx® Schering Plough Pharmaceuticals) combined with CDDP and RT for uterine cervix carcinoma.
Materials and Methods: 24 patients with stage IIB–IVA were enrolled. They all received external RT (up to 50.4 Gy) and two medium-dose rate (MDR) brachytherapy implants (20 Gy each at point A). The Caelyx starting dose of 7 mg/m^2/week was increased in 5-mg/m^2 increments to two levels. The standard dose of CDDP was 20−25 mg/m^2/week.
Results: Concurrent chemoradiation (CCRT) sequelae and the DLTs as grade 3 myelotoxicity and grade 3 proctitis were observed in five patients treated at the 17 mg/m^2/week Caelyx dose level. After a median follow-up time of 17.2 months (range 4−36 months), four patients had died, 15 showed no evidence of progressive disease, and five (20.8%, 95% confidence interval [CI]: 12.5−29.1%) were alive with relapse. There were seven complete (29.1%, 95% CI: 19.8−38.4%) and 17 partial clinical responses (95% CI: 61.1−80.1%). The median progression-free survival was 10.4 months. Causes of death were local regional failure with or without paraaortic node relapse combined with distant metastases.
Conclusions: The MTD of Caelyx given concurrently with CDDP and RT was determined at the 12 mg/m^2/week dose level. The above CCRT schedule is a well-tolerated regimen, easy to administer in ambulatory patients, and results appear promising.

5033 POSTER

Feasibility and pharmacokinetics of intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) with paclitaxel following cytoreductive surgery in ovarian cancer patients

E. de Bree[1], H. Rosing[2], D. Filis[1], J. Romanos[1], M. Melissourgaki[1], M. Daskalakis[1], M. Pilatou[1], E. Sanidas[1], J.H. Beijnen[2], D.D. Tsiftsis[1]. *[1]Medical School of Crete University Hospital, Dept. of Surgical Oncology, Herakleion, Greece; [2]Slotervaart Hospital/The Netherlands Cancer Institute, Dept. of Pharmacy and Pharmacology, Amsterdam, The Netherlands*

Background: Intraperitoneal chemotherapy has been recommended after optimal surgical cytoreduction in patients with stage III ovarian cancer. The potential advantages of intraoperative above postoperative intraperitoneal chemotherapy are superior exposure of the drug to the entire seroperitoneal surface, the possibility of combination with hyperthermia, which is cytotoxic itself and enhances the efficacy of many drugs, and avoidance of dysfunction and infectious complications of peritoneal access devices. Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer is usually performed with cisplatin. The use of paclitaxel, highly effective in systemic chemotherapy in ovarian cancer, has not been previously reported. We studied the feasibility and pharmacokinetics of HIPEC with paclitaxel in ovarian cancer patients.
Material and Methods: Ten patients with stage III ovarian cancer were treated with cytoreductive surgery followed by HIPEC with paclitaxel. Their median age was 62 years (28−73). After cytoreductive surgery and temporary closure of the abdominal wall, the peritoneal cavity was perfused with 175 mg/m^2 paclitaxel (Taxol®, Bristol-Myers Squibb) in 4−7 liters normal saline for 2 hours at an intraperitoneal temperature of 41−43ºC. Surgical complications and drug toxicity were recorded. Plasma and peritoneal fluid samples were harvested for pharmacokinetic study during and until 5 days after HIPEC. Samples were analyzed by HPLC-MS/MS using an Electrospray ionisation interface and positive-ion multiple reaction monitoring.
Results: One patient developed deep venous thrombosis and wound infection, while two patients exhibited drug related toxicity. One patient demonstrated grade 2 neutropenia and another patient, heavily pretreated with systemic chemotherapy, grade 3 pancytopenia. No treatment related mortality occurred. Pharmacokinetic data were available for 7 patients. The mean maximal intraperitoneal drug concentration was 112.0 μmol/L (38.9–213.1), while the mean maximal peritoneal fluid versus plasma paclitaxel

concentration ratio was 959. Cytotoxic concentrations of >0.1 μmol/L were detected in peritoneal fluid for a median period of 4 days (1−4) after HIPEC.
Conclusions: Cytoreductive surgery followed by HIPEC with paclitaxel seems feasible in stage III ovarian cancer patients. HIPEC with paclitaxel is associated with a highly advantageous pharmacokinetic profile. Locoregional drug concentrations are in the micromolar range rather than in the nanomolar range as for plasma levels after intravenous administration, while cytotoxic drug levels are maintained in the peritoneal cavity for several days after HIPEC.

5034 POSTER

Pharmacokinetics of trabectedin in women with recurrent ovarian cancer

J.M. del Campo[1], B. Pardo[2], A. Cervantes[3], A. Gonzalez[4], A. Parera[1], C. Cuadra[2], C. Lebedinsky[5], B. Miguel-Lillo[5], A. Soto-Matos[5], M.A. Izquierdo[5]. *[1]Hospital Vall'Hebron, Oncología, Barcelona, Spain; [2]Instituto Catalan de Oncologia, Oncología, Llobregat, Spain; [3]Hospital Clínico de Valencia, Oncología, Valencia, Spain; [4]Hospital Ramon y Cajal, Oncología, Madrid, Spain; [5]PharmaMar, Clinical, Madrid, Spain*

Background: Trabectedin (Yondelis®, ET-743) is an anticancer compound that has shown clinical activity in soft tissue sarcoma (STS), ovarian, prostate and breast cancer. Pharmacokinetics (PK) of trabectedin has been well defined in patients with STS and in other solid tumours during the Phase I and II program. This report describes the PK behaviour of trabectedin in women with platinum-sensitive, recurrent ovarian cancer (ROC) included in a Phase II study.
Methods: Adult women with ROC were randomised to receive trabectedin as 1.5 mg/m^2 over 24 hr infusion (schedule A) or 1.3 mg/m^2 over 3 hr infusion (schedule B) both every 3 weeks. All patients received dexamethasone premedication. Fourteen plasma samples were obtained within 168 hr after starting the first infusion. An LC/MS/MS assay was used to measure trabectedin in plasma. PK parameters were estimated by standard noncompartmental methods.
Results: The PK of trabectedin was characterised in 18 patients (11 schedule A, 7 schedule B) with adequate renal and hepatic function, and a median age of 58 y (range 41−72 y). Mean (SD) C_{max} and AUC_{inf} were 1.4 (0.7) ng/ml and 59.7 (27.2) ng*hr/ml for schedule A and 12.1 (6.4) and 73.6 (41.7) for schedule B. Mean (SD) Cl and V_{ss} were 47.4 (12.2) l/hr and 3848 (2319) l for schedule A and 38.2 (16.2) and 2698 (1423) for schedule B. Half-life was 95.8 (46.3) hr for schedule A and 96.1 (45.4) for schedule B. Interpatient variability was moderate/high, with variation coefficients ranging from 26% to 60%. Patients with grade 3−4 neutropenia during cycle 1 had longer half-lives than patients with grade 0−2. Patients with grade 3−4 ALT increases had higher C_{max} than patients with grade 0−2. Response rates (RR) were 44% and 36% in patients with (n = 18) and without PK (n = 89) respectively. Half-lives in responding patients showed a trend to be longer than those in nonresponders. Results about PK/PD relationships should be interpreted considering the low sample size. PK results with schedule A matched closely those from a prior study in STS patients [C_{max} = 1.22 (0.48), AUC_{inf} = 65.0 (37.8), half-life = 138.3 (109.2)]. Mean C_{max} in schedule B appeared higher than that in a prior Phase I trial [C_{max} = 6.41 (SD = 1.49; n = 6)].
Conclusions: PK characteristics of trabectedin in patients with ROC are in line with those observed in patients with other malignancies, showing a long terminal half-life, wide distribution, moderate total body clearance and moderate/high interpatient variability.

5035 POSTER

A protective role of magnesium salt supplementation against anaemia induced by paclitaxel and cisplatin in ovarian cancer (OC) patients

L. Bodnar, G. Wcislo, A. Synowiec, A. Cieslak, C. Szczylik. *Military Institute of the Health Services, Department of Oncology, Warsaw, Poland*

Background: Paclitaxel and cisplatin are both well accepted drugs used in the treatment of ovarian cancer (OC) and anemia appears to be one of side effects. Cisplatin is a culprit of anemia by erythropoietin deficiency. We assessed the endogenous erythropoietin concentrations and other red blood cells parameters in OC patients given chemotherapy with magnesium salt supplementation vs. placebo.
Patients and Methods: A double-blind, placebo-controlled, randomised study conducted where magnesium sulphate was administered at a dose of 5 g as an iv infusion before each course of chemotherapy with PP (paclitaxel 135 mg/m^2 over 24 h infusion plus cisplatin 75 mg/m^2) every 3 weeks. Magnesium subcarbonate continuation at a dose of 500 mg given three times daily p.o. among courses. We performed analysis of serum concentrations of erythropoietin, haemoglobin and magnesium before treatment and before sixth course of chemotherapy.
Results: Between February 2003 and January 2006, 40 OC patients were enrolled. None of the patients received recombinant human erythropoietin or red blood cell transfusion. Haemoglobin levels decreased from 12.07±1.03 g/dl (mean±SE) (control 11.75±1.03 g/dl; p = 0.344) before treatment to 11.10±1.17 g/dl (control 10.04±1.17; p = 0.009) before sixth cycles in study group. Erythropoietin serum concentrations weren't changed significantly in both groups. Mg serum concentrations decreased significantly from 2.12±0.10 mg/dl to 1.63±0.19 mg/dl before sixth cycles (p < 0.0001) in placebo group.
Conclusions: Our results indicate that magnesium salt supplementation during chemotherapy may decrease anemia independently of erythropoietin serum changes.

5036 POSTER

Tumor advancement in uterine endometrial cancers patients

L. Bolokadze. *31 City Hospital, Gynaecological Oncology, Kharkov, Ukraine*

Objective: The aim of this study was to investigate the expression of ephrinB2 and EphB4 in uterine endometrial cancers to analyze the ephrinB2/EphB4 functions against clinical backgrounds.
Methods: In 53 uterine endometrial cancers and 18 normal endometrium tissue samples immunohistochemistry and real-time RT-PCR to determine the histoscores and messenger RNA (mRNA) levels of ephrinB2 and EphB4, respectively, were carried out. Patient prognoses were analyzed with a 5-years survival rate.
Results: The localization of ephrinB2 and EphB4 was dominantly in the cancer cells of uterine endometrial cancer of all investigated cases. EphrinB2 and EphB4 histoscores were highly correlated with ephrinB2 and EphB4 mRNA levels, respectively (P < 0.01). Both the histoscores and mRNA levels of ephrinB2 and EphB4 significantly increased with clinical stages (I < II < III, P < 0.05), dedifferentiation (G1 < G2 < G3, P < .01) and myometrial invasion (A < B < C, P < .01 for ephrinB2 and P < 0.05 for EphB4) in uterine endometrial cancers. The 5-years survival rates of the 24 patients with high ephrinB2 and EphB4 expression were poor (57% and 63% respectively), for the 29 patients with low ephrinB2 and EphB4 expression, they were significantly higher (83% and 84%, respectively).
Conclusions: EphrinB2 and EphB4 were overexpressed during the tumor advancement as dedifferentiation and myometrial invasion. EphrinB2/EphB4 might work on tumor advancement and could be recognized as a novel prognostic indicator for uterine endometrial cancers.

5037 POSTER

Pelvic node control in locally advanced uterine cervical cancer treated with concurrent chemoradiotherapy

T. Toita[1], W. Tamaki[1], Y. Nagai[2], K. Ogawa[1], S. Gibo[1], Y. Kakinohana[1], M. Hirakawa[2], K. Kamiyama[2], Y. Aoki[2], S. Murayama[1]. *[1]Graduate School of Medical Science University of the Ryukyus, Radiology, Okinawa, Japan; [2]Graduate School of Medical Science University of the Ryukyus, Obstetrics and Gynecology, Okinawa, Japan*

Background: Several investigators recommend surgical debulking of enlarged lymph nodes prior to definitive radiotherapy for patients with locoregionally advanced uterine cervical cancer. The purpose of this study was to evaluate pelvic node control in patients with cervical cancer treated with concurrent chemoradiotherapy (CCRT) without surgical resection.
Material and Methods: Ninety-nine patients with uterine cervical squamous cell carcinoma treated with CCRT were analyzed. The stage distributions were: IB2 3; IIA 2; IIB 50; IIIA 1; IIIB 42; and IVA 1. Cervical tumor diameter and pelvic node status were assessed by MRI. The median maximum tumor diameter was 58 mm (range, 36−86 mm). Thirty-five patients had positive pelvic nodes (⩾10 mm, in the shortest diameter). The largest positive node diameter ranged from 10−50 mm (median, 18 mm). All patients received CDDP (20 mg/m^2 for 5 days every 21 days), pelvic external beam RT (PERT), and high-dose-rate intracavitary brachytherapy (HDR-ICBT). The planned RT schedule consisted of PERT with 40 Gy/20 fractions followed by HDR-ICBT with 18−24 Gy/3−4 fractions and PERT with 10 Gy/5 fractions using a midline block. Thirty-one of the thirty-five node positive patients received boost irradiation (6−10 Gy/3−5 fractions) to the involved nodes. The irradiation dose from HDR-ICBT to the pelvic nodes was estimated at a point 6 cm lateral to the midline at the level of the vaginal fornix. Doses of ERT and HDR-ICBT were simply summed and used for the pelvic node dose-response analysis. The median total dose was 60 Gy (range, 52−64 Gy) for positive nodes and 54 Gy (range, 51−55 Gy) for negative nodes. The median follow-up of the 81 surviving patients was 50 months (range, 8–102 months).
Results: Four-year overall survival (OAS), pelvic control (PC), and distant metastasis-free (DMF) rates for all 99 patients were 81%, 91%, and 80%, respectively. Four-year OAS, PC, and DMF rates for node-positive/node-negative patients were 62%/91% (P = 0.002), 82%/95% (P = 0.08), and