(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.

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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.

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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