Results: Median age was 59 years (range 35–78) for cohort 1 and 57 years (range 35–83) for cohort 2. Median ECOG PS was 1 (range 0–3) for cohort 1 and 0 (range 0–1) for cohort 2. The median number of prior chemotherapy regimens was 5 for both cohorts. 60 pts. in cohort 1 and 62 pts. in an interim analysis of cohort 2 were evaluable for response. There were a total of 5 objective partial responses (PRs) (RR = 4%), 2 in cohort 1 and 3 in cohort 2. 7 pts. (6%) had SD with CA-125 reduction of ⩾50% (4 in cohort 1, 3 in cohort 2). An additional 3 pts (2%) had SD for ⩾6 months (all in cohort 1, cohort 2 data still premature). Overall rate of activity = 12%. Overall median time to progression (TTP) was 6.6 weeks (7.0 weeks in cohort 1, 6.6 weeks in cohort 2). Of the 65 tumor biopsies from cohort 1, 31 were evaluable and 8 (26%) were positive for pHER2 by ELISA. TTP for pHER2+ pts. was 20.9 weeks (n = 8), compared to 6.0 weeks for pHER2 – (n = 23), and 9.1 weeks for unknown pHER2 status (n = 29). P was well tolerated with diarrhea in 61% of pts (grade 1–3) (57% in cohort 1, 65% in cohort 2). 5 pts. had a drop in ejection fraction to <50% with 1 confirmed by a central facility.
Conclusions: As a single agent P is well tolerated. Clinical activity was observed in 12% of pts with heavily pretreated OC as demonstrated by PRs, SD ⩾6 months, and SD with CA-125 reductions of ⩾50%. This study suggests P may be active in OC. Preliminary analysis suggests pHER2 status may be important for P activity.

904 ORAL

Adjuvant treatment of early stage cervix cancer: a systematic quantitative review

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Background: Patients with early stages cervix cancer (IA_2-IIA) with postoperative findings of lymph node metastasis, lymphovascular space invasion, depth of invasion more than 10 mm, parametrial invasion, non-squamous histology, or positive surgical margins are at increased risk for subclinical dissemination of the disease. Postoperative radiotherapy has been found to decrease the incidence of local recurrence with little or no effect on overall survival. This review has been undertaken to assess the available evidence for adding chemotherapy to radiotherapy in the adjuvant treatment of those patients.
Material and methods: We have searched the Cochrane Library, CENTRAL, MEDLINE, EMBASE, LILACS, Biological Abstracts, CINAHL, SciSearch and Cancerlit. We have handsearched the congress proceedings of cancer societies. All randomised controlled trials comparing postoperative chemotherapy and radiotherapy (intervention group) with postoperative radiotherapy alone (control group) in the treatment of stages IA_2-IIA cervix cancer were included. Outcome measures were overal survival, progression-free survival, local recurrence, distant recurrence, major treatment toxicities (grades 3 and 4) and quality of life.
Results: We found 10 randomised controlled trials, but only two met the selection criteria, including a total of 314 patients. Overall survival: Patients in the intervention group had a significantly reduced hazard of death in 48 months (HR 0.43, 95% CI 0.25 to 0.76). Progression-free survival: At 48 months the hazard ratio was estimated to be 0.45 (95% CI 0.28 to 0.74). Local recurrence: At 48 months, there was less local recurrence in the intervention group (HR 0.50; 95% CI 0.26 to 0.98). Distant recurrence: There was no difference between the intervention and the control groups in the hazard of distant recurrence at 48 months (HR 0.74; 95% CI 0.36 to 1.52). Major toxicities: The odds for grade 3 and 4 major toxicities was significantly higher in the intervention group (Peto OR 5.19 [95% CI 2.90 to 9.29] and 4.62 [95% CI 1.96 to 10.86], respectively). We were unable to obtain data about quality of life.
Conclusions: In this systematic review, the overall evidence suggests that the addition of chemotherapy in the adjuvant treatment of early stage cervix cancer with risk factors for recurrence provides clinical benefit. However, the evidence is limited because the selected studies were quantitatively and qualitatively limited, with small number of patients and limited time of follow-up. There is a need for further randomised controlled trials to compare adjuvant chemotherapy and radiotherapy with adjuvant radiotherapy alone in the treatment of early stage cervix cancer with risk factors for recurrence. This review is registered in the Cochrane Gynaecological Cancer Group (H011).

905 ORAL

A randomized phase III trial of concurrent chemoradiation in locally advanced cervical cancer: preliminary results

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Background: Concurrent chemoradiation by platinum based is the standard treatment for locally advanced cervical cancer. Carboplatin is platinum analogue which has comparable activity with cisplatin. 5FU is the drug that has synergistic effect with radiation. The therapeutic index of 5FU is improved when given as a continuous intravenous infusion. Tegafur-Uracil (UFT®) is an oral chemotherapy which is recommended to replace the continuous intravenous infusion of 5FU as a radiosensitizer. This study was a preliminary result of a randomized two arms, prospective, open-label phase III trial comparing the activity and safety of the concurrent chemoradiation of UFT & carboplatin or carboplatin alone in locally advanced cervical cancer.
Materials and Methods: The stage IIB-IIIB cervical cancer patients were randomized to have UFT 225 mg/m^2/day orally and carboplatin 100 mg/m^2 IV over 30–60 minutes, weekly on day 1 concurrent with standard radiotherapy (UFT group) or carboplatin alone concurrent with standard radiotherapy (control group). In UFT group, UFT was taken in 3 divided doses daily at the same day of radiotherapy, 5 days a week and stopped on weekend. The tumor response and toxicity were evaluated weekly during treatment, 1 month interval for 3 months and 3–6 months for 5 years.
Results: From July 2001 to December 2003, 469 patients were randomized to UFT group (n = 234) or control group (n = 235). There was no significant imbalance in patient characteristics. The treatment interruption and the dose modification were nearly the same in both groups. The tumor response at 3 months follow up time was no significant difference. The only prognostic factor to improve the complete response rate was the hemoglobin (Hb) level. The patients in UFT group who had Hb < 10 gm/dl had the relative risk to complete response 1.48 compared to that in control group (P = 0.025, 95% CI 1.07, 2.04). The severe toxicity or adverse event had not been reported. The median follow up time for UFT group and control group were 12.6 and 11.8 months, respectively. There was no statistical difference in PFS and OS.
Conclusion: Concurrent chemoradiation by UFT and carboplatin was not difference in tumor response rate or treatment toxicity compared to carboplatin alone. The combination drugs might have benefit in poor prognostic patients such as the baseline Hb < 10 gm/dl.

906 ORAL

A differential gene expression profile reveals RUNX1/AML1 and ERM/ETV5 up-regulation correlating to infiltration stages in endometrioid endometrial carcinoma

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Background: endometrial cancer (EC) is the most common gynaecological cancer in industrialized countries. Among the different subtypes, type I or endometrioid EC (EEC) represents the 80% of its incidence. It is associated with oestrogen exposition and affects mainly peri- and post-menopause young women. Good prognosis is related with early diagnosis and uterus localization. In this context, myometrial affectation as the initial event of tumour invasion and distant dissemination, determines an increase in recurrences after a first surgical treatment, and a decrease in the five years survival. Studies focused on the molecular basis of EC have demonstrated correlations among molecular alterations (PTEN gene silencing, microsatellite instability associated with defects in DNA mismatch repair genes, or mutations in the K-ras gene) and tumour progression, its molecular pathology remaining essentially unknown.
Material and methods: identification of molecular factors responsible of endometrial tumorigenesis by cDNA microarrays. Validation of the candidate genes by Real-Time quantitative PCR and tissue arrays.

Results: we have identified a panel of 53 sequences differentially expressed in EEC when compared to healthy endometrium. Among these, the transcription factors RUNX1/AML1 and ERM/ETV5 have been studied in detail and their expression significantly related with the early myometrial infiltration phase (stage IC). Moreover, increased ERM/ETV5 expression was associated with matrix-degrading metalloprotease-2 (MMP2) activity, and ERM/ETV5 up-regulation correlated to that of RUNX1/AML1.
Conclusions: We propose a cooperative role between RUNX1/AML1 and ERM/ETV5 during the early events of endometrial tumorigenesis, which may be associated with an initial switch to myometrial infiltration. The further characterization of the mechanism of action of both genes during endometrial tumorigenesis will contribute with the clues of the initial mechanisms of invasion and dissemination in EEC, their validation as early markers of myometrial invasion and metastasis in EEC, and to design and evaluate preclinical assays based on the characterization of potential therapeutic targets.

907 ORAL

A Phase II study of Temsirolimus (CCI-779) in patients with metastatic and/or recurrent endometrial cancer – NCIC CTG IND 160

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Background: PTEN is a tumor suppressor gene and mutations in PTEN leading to loss of protein expression/function appear to play a significant role in the pathogenesis of endometrial carcinoma based on laboratory and clinical studies. In various series, loss of PTEN protein expression, occurs in 26–80% of endometrial carcinomas in various series. Loss of PTEN function leads to deregulated PI3K/Akt/mTOR signalling, an event that is thought to provide neoplastic cells with a selective survival advantage by enhancing angiogenesis, protein translation and cell cycle progression. Inhibition of mTOR, a protein kinase downstream of the PI3K/Akt pathway and target of rapamycins, inhibits proliferation of endometrial carcinoma cell lines and formation of endometrial neoplasias including carcinomas in PTEN± heterozygous mice. Given the frequent loss of PTEN in human endometrial carcinomas, and the anti-tumour activity induced with mTOR inhibition, temsirolimus an ester derivative of rapamycin that inhibits mTOR was evaluated in this setting.
Methods: A 2 stage, phase II study is underway to evaluate single agent activity of temsirolimus in endometrial cancer. Women with recurrent or metastatic endometrial cancer, who are chemotherapy naïve and have received up to one prior line of hormonal therapy, are eligible. Treatment is given at a dose of 25 mg weekly. One cycle is defined as 4 weeks of therapy. Eighteen patients have been registered to date, and 15 are evaluable for toxicity and 14 for response. Eleven had received prior radiation and seven hormonal therapy. Sixteen patients had adenocarcinoma and 2 had adeno-squamous carcinoma; 14 patients had grade 2/3 disease.
Results: Hematologic toxicity has been mild with 6 episodes of grade 3 lymphopenia; 4 patients had grade 3 non-hematologic adverse events [hypotension, rash, GI, neuropathy, pain] and 1 patient had grade 5 renal failure [secondary to dehydration and CT contrast]. There have been no grade 3 or 4 biochemical toxicities. Three patients have had a confirmed partial response (21%) and 10 patients have stable disease (71%). One patient had progressive disease (7%). Results will be correlated with PTEN status. Using multinomial endpoints incorporating response and stable disease, the study has met the pre-defined requirements for expansion to the second stage.
Conclusions: The preliminary results suggest encouraging single agent activity for temsirolimus in recurrent and metastatic endometrial cancer.

Poster presentations (Tue, 1 Nov)
Gynaecological cancer

908 POSTER

A Randomised Phase II study of Phenoxodiol with platinum or taxane chemotherapy in chemoresistant epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer

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Background: Despite high rates of response to initial chemotherapy, most patients with ovarian cancer relapse with chemoresistant disease. The development of platinum- and taxane-resistance is associated with over-expression of anti-apoptotic factors. Phenoxodiol (PXD, 2H-1-benzopyran-7−0, 1, 3-[4-hydroxylphenyl]) a flavonoid derivative synergizes the cytotoxicity of platinums, taxanes and gemcitabine in chemosensitive ovarian cancer cells. *In vitro* PXD-induces apoptosis in chemoresistant ovarian cancer cells and restores chemo-sensitivity to platinum, taxanes and topotecan in chemo-resistant ovarian cancer cells. These data support the study of PXD in chemoresistant ovarian cancer.
Methods: Eligible patients (pts) had recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer with rising CA125 within 6 months of prior therapy. Pts had <4 prior chemotherapy regimens, measurable disease and Karnofsky performance status >60%. Pts were randomised to receive PXD (3 mg/kg) days 1 and 2 and either cisplatin (40 mg/m^2) or paclitaxel (80 mg/m^2) on day 2 until disease progression or prohibitive toxicity. Primary endpoints were response rate by RECIST (Therasse *et al.*, 2000) and GCIG criteria (Rustin *et al.*, 2004), progression free survival (PFS) and toxicity by NCI criteria.
Results: Forty patients have been randomised (20 to PXD+CDDP, 20 to PXD+Paclitaxel) and 36 are evaluable for response. Median age was 56 (45–72) and median number of prior chemotherapy regimens was 3 (1–4). Complete response (CR) was observed by RECIST in 4 pts (11%), partial response (PR) in 8 pts (22%) and stable disease (SD) in 15 pts (42%) for an overall clinical benefit in 75%. Nine patients had disease progression within 6 weeks of randomisation. Objective tumor responses (CR+PR) were observed in 43% of pts where prior platinum or taxane free interval was >12 months and 25% when PFI/TFI was <12 months.. Toxicity was related to chemotherapy with no additional toxicity observed. Toxicity and QOL data will be presented.
Conclusions: Preliminary results indicate that PXD administered with chemotherapy results in high response rates among women with chemoresistant epithelial ovarian cancer.

909 POSTER

Phase I/II dose-escalation trial of patupilone every 3 weeks in patients with resistant/refractory ovarian cancer

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Background: The current standard of care for patients with newly diagnosed advanced ovarian cancer is therapy with a platinum and taxane-based combination regimen. However, patients who are refractory or resistant to the regimen have a poor prognosis. Patupilone, a natural epothilone, is a microtubule-targeting agent that has demonstrated clinical activity in taxane-sensitive and -resistant tumors. We are investigating the safety and efficacy of patupilone in patients with advanced ovarian cancer who failed to respond to or relapsed within 6 months of first-line platinum therapy.
Material and methods: Patients received patupilone at a starting dose of 6.5 mg/m^2 via 10- to 20-minute IV infusion once every 3 weeks (q3w) with proactive diarrhea management.
Results: To date, 45 patients have been enrolled in 10 cohorts receiving 6.5 (n = 3), 7.0 (n = 3), 7.5 (n = 3), 8.0 (n = 6), 8.5 (n = 3), 9.0 (n = 6), 9.5 (n = 6), 10.0 (n = 6), 10.5 (n = 3), and 11.0 (n = 6) mg/m^2 patupilone. Currently, 32 patients are eligible for assessment; 94% had received prior taxane therapy. Dose-limiting toxicities were reported in the 8.0 and 8.5 mg/m^2 cohorts: 1 patient in each cohort had grade 3 fatigue. Grade 4 serum uric acid precipitated by an ileus, grade 3 hypomagnesemia, and grade 3 diarrhea were reported on day 21 of the first cycle by a patient enrolled in the 9.0 mg/m^2 cohort. Because these toxicities were deemed unrelated to study drug, the cohort was expanded and no further dose-limiting toxicities were reported. Dose escalation continued up to the 11.0 mg/m^2 cohort, wherein grade 3 diarrhea was reported by 1 patient. Overall, 19% of patients reported grade 3 diarrhea and 9% reported grade 3 fatigue. Eleven (34%) patients had grade 1/2 neuropathy/paresthesia and 1 heavily pretreated (19 platinum cycles) patient had grade 3 neuropathy/paresthesia. Alopecia was infrequent and mild in severity. Hematologic toxicity was rare. Dose escalation was halted at 11.0 mg/m^2 and, based on acute and chronic toxicities, the recommended phase II dose was determined to be 10.0 mg/m^2 patupilone. Thirty-two patients were evaluable for tumor response by Response Evaluation Criteria in Solid Tumors: 1 had a complete response, 7 had a partial response, and 8 had stable disease.